11-19-90

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 19 1990

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: PP#9F3775/FAP#9H5583 - Quinclorac New Chemical Registration Request to Establish Tolerances for Quinclorac (FACET® Herbicide, EPA File Symbol 7969-OG) in/on Rice with Associated Tolerances in Meat, Milk, and Eggs

TOX Chem No.: 325A
Project No.: 9-1764A
Record No.: 243011

FROM: William B. Greear, M.P.H. William B. Greear 10/16/90
Review Section II
Toxicology Branch I Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Marion P. Copley, D.V.M., Section Head KB 11/15/90
Review Section II
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

I. CONCLUSIONS

Toxicology Branch I (TB-I) has determined that the toxicological data base on quinclorac is inadequate and will not support the establishment of permanent tolerances. TB-I concurs with the Science Analysis and Coordination Branch (SACB) memorandum dated July 13, 1989 that the 21-day dermal study on the technical may be waived.

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II. ACTION REQUESTED

Under a cover letter dated March 21, 1989, Robert W. Rhode of the BASF Corporation has requested that tolerances be established for residues of quinclorac (3,7-dichloro-8-quinolinecarboxylic acid) in/on the following commodities:

Commodities	Tolerances (ppm)
Rice	5.00
Rice straw	12.00
Milk	0.05
Cattle, fat	0.05
Cattle, meat	0.05
Cattle, mbyp	0.05
Goats, fat	0.05
Goats, meat	0.05
Goats, mbyp	0.05
Hogs, fat	0.05
Hogs, meat	0.05
Hogs, mbyp	0.05
Horses, fat	0.05
Horses, meat	0.05
Horses, mbyp	0.05
Eggs	0.05
Poultry, fat	0.05
Poultry, meat	0.05
Poultry, mbyp	0.10
Sheep, fat	0.05
Sheep, meat	0.05
Sheep, mbyp	0.05
Rice bran	15.00

In addition, the sponsor requests a section 3 registration for the use of FACET® Herbicide on rice.

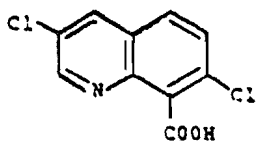
It was also requested that the requirement for a Guideline Series 82-2 - 21-Day Repeated-Dose Dermal Study on the technical be waived.

The following studies were submitted to TB-I in support of the requested action (Data Evaluation Reports DERs are attached).

Guideline Series	Study	MRID No.
81-1	Acute Oral Toxicity - Rat	410635-05
81-1	Acute Oral Toxicity - Rat	410635-06
81-1	Acute Oral Toxicity - Mouse	410635-07
81-2	Acute Dermal Toxicity - Rat	410635-09
81-3	Acute Inhalation Toxicity - Rat	410635-10
81-4	Primary Eye Irritation - Rabbit	410635-11
81-5	Primary Dermal Irritation - Rabbit	410635-12
82-1	90-Day Feeding - Rat	410635-16
	4-Week Range Finding - Rat	410635-14
	4-Week Range Finding - Rat	410635-15
82-1	90-Day Feeding - Mouse	410635-18
	4-Week Range Finding - Mouse	410635-17
83-1	12-Month Feeding - Dog	411232-01
	4-Week Range Finding - Dog	410635-20
83-2	78-Week Carcinogenic - Mouse	410635-23
83-3	Developmental Toxicity - Rat	410635-24
83-3	Developmental Toxicity - Rabbit	410635-25
83-4	2-Generation Reproduction - Rat	410635-26
83-5	Combined 2-Year Chronic Feeding/ Carcinogenic - Rat	410635-22
84-2	Gene Mutation - (Ames)	410635-27
84-2	Gene Mutation - (Reverse Mutation)	410635-28
84-2	Gene Mutation - (CHO/HGPRT)	410761-02
84-2	Structural Chromosomal Aberration (*In Vitro* Cytogenetics)	410761-03
84-2	Structural Chromosomal Aberration (*In Vivo* Cytogenetics)	310635-30
84-2	Structural Chromosomal Aberration	410635-29
84-2	Other Genotoxic Effects (Micronucleus)	410635-32
84-2	Other Genotoxic Effects - (UDS)	410635-31
85-1	General Metabolism - Rat	410635-33
Other	Acute Intraperitoneal Toxicity - Rat	410635-08

III. PRODUCT INFORMATION (Updated October 1990)

Quinclorac is a herbicide with the chemical name of 3,7-dichloro-8-quinolinecarboxylic acid and proprietary name of FACET® Herbicide or Impact® Herbicide which is a 50 percent active ingredient wettable powder. Its chemical structure is as follows:



Quinclorac has previously been approved for use on rice to control weeds under an experimental use permit (EUP).

IV. REQUIREMENTS FOR A REGISTRATION (TERRESTRIAL NONFOOD USE) [CFR 158.340]

Quinclorac, #325A
Updated October 1993

Facet® Herbicide	Required	Satisfied
Formulation		
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y
Technical		
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y
81-7 Acute Delayed Neurotoxicity (Hen)	N	-
82-1 Subchronic Oral (Rodent)	Y	Y
82-1 Subchronic Oral (Nonrodent)	Y	Y[1]
82-2 21-Day Dermal	Y	W[2]
82-3 90-Day Dermal	N	-
82-4 90-Day Inhalation	N	-
82-5 90-Day Neurotoxicity (Hen)	N	-
82-5 90-Day Neurotoxicity (Mammal)	N	-
83-1 Chronic Toxicity (Rodent)	Y	N
83-1 Chronic Toxicity (Nonrodent)	Y	Y
83-2 Carcinogenicity (Rat)	Y	N
83-2 Carcinogenicity (Mouse)	Y	Y
83-3 Developmental Toxicity (Rat)	Y	Y
83-3 Developmental Toxicity (Rabbit)	Y	N
83-4 Reproduction	Y	N
83-5 Chronic/Carcinogenic	-	-

Y = Yes; N = No; W = Waiver

[1]The 1-year chronic study in dogs is acceptable in lieu of the subchronic study.

[2]SACB has recommended that the requirement for this study be waived (see memorandum of D.G. Van Ormer dated July 13, 1989). TB-I concurs.

Quinclorac, #325A
Updated October 1990

Technical (cont'd)	Required	Satisfied
84-2 Mutagenicity - Gene Mutation	Y	Y
84-2 Mutagenicity - Structural Chromosomal Aberration	Y	Y
84-2 Mutagenicity - Other Genotoxic Effect	Y	Y
85-1 General Metabolism	Y	Y
85-2 Dermal Penetration	N	-
86-1 Domestic Animal Safety	N	-

Y = Yes; N = No

V. TOXICOLOGY PROFILE

Study; Classification; Toxicity Category; Study Number; Date	Quinclorac, No. 325A Updated: October 1990
Technical Quinclorac	**Results**
81-1 Acute Oral LD_{50} - Rat; Guideline; III; 83/0240; December 12, 1983	LD_{50} = 3060 mg/kg (male) LD_{50} = 2190 mg/kg (female)
81-2 Acute Dermal LD_{50} - Rat; Minimum; III; 83/0244; December 12, 1983	LD_{50} > 2000 mg/kg
81-3 Acute Inhalation LC_{50} - Rat; Guideline; III; 85/0271; August 20, 1985	LC_{t50} > 5.2 mg/L; t = 4 hrs
81-4 Primary Eye Irritation - Rabbit; Guideline; III; 83/0170; August 18, 1983	Mild irritation, clearing by day 8
81-5 Primary Dermal Irritation - Rabbit; Guideline; IV; 83/0169; August 18, 1983	Not an irritant
81-6 Dermal Sensitization - Guinea Pig; Guideline; 86/0117; May 6, 1986	Positive sensitizer
82-1 90-Day Subchronic Oral - Rat; Supplementary; 38/5145; March 13, 1986	NOEL = 4000 ppm (M = 302.3 and F = 358.0 mg/kg/day) LEL = 12000 ppm (M = 929.0 and F = 1035.4 mg/kg/day)

Toxic Effects - Decreased food consumption, body weight gain, and HCT HGB, MCH, and lymphocytes in females; increased water intake, increased monocytes and neutrophilic segmented granulocytes in females, SGOT and SGPT in males, and minimal to slight focal interstitial nephritis in males.

83-1 1-Year Chronic Oral - Dog; Guideline; 88/0029; January 6, 1988	NOEL = 4000 ppm (140 mg/kg/day LEL = 12000 ppm (513 mg/kg/day males; 469 mg/kg/day females

Toxic Effects - Decreased body weight gain and food efficiency, HGB, RBC HCT, MCV, and MCH, increased absolute and relative liver weight, focal mononuclear infiltration and single cell necrosis in the liver and hydropic degeneration of the kidney.

83-1 Rat - see 83-5

83-2 Rat - see 83-5

Study; Classification; Toxicity Category; Study Number; Date	Quinclorac, No. 325A Updated: October 1990
Technical Quinclorac (cont'd)	Results
83-2 18-Month Carcinogenicity - Mouse; Guideline; 88/5114; September 14, 1988	Negative for carcinogenicity

Toxic Effects - Decreased body weight at 1000, 4000, and 8000 ppm; decreased absolute liver weight at 8000 ppm; decreased absolute/relative kidney weight in males at 1000, 4000, and 8000 ppm.

83-3 Developmental Toxicity - Rat; Minimum; 88/0167; May 12, 1987	NOEL (maternal) = 146 mg/kg LEL (maternal) = 438 mg/kg (decreased food consumption, increased water intake and mortality) NOEL (developmental) = 438 mg/kg/day (HDT)

Toxic Effects - Decreased food consumption, increased water intake and mortality in dams at 438 mg/kg (HDT). No effects noted at 24.4 and 146 mg/kg.

83-3 Developmental Toxicity - Rabbit; Supplementary; 88/0099; April 5, 1988	NOEL/LEL could not be determined.

Toxic Effects - Decreased food consumption and body weight gain, increased water intake, mortality, and discoloration of the kidney at [illegible] mg/kg/day (HDT). No effects noted at 70 and 200 mg/kg.

83-4 2-Generation Reproduction - Rat; Supplementary; 88/0321; July 21, 1988	NOEL (maternal) = 4000 ppm (160 mg/kg/day) LEL (maternal) = 12000 ppm (480 mg/kg/day) NOEL (developmental) = 4000 ppm (160 mg/kg/day) LEL (developmental) = 12000 ppm (480 mg/kg/day)

Toxic Effects - Decreased body weight of dams, pup viability, and pup weight, and delay in development, i.e., pinna unfolding and eye opening.

Study; Classification; Toxicity Category; Study Number; Date	Quinclorac, No. 325A Updated: October 1990
Technical Quinclorac (cont'd)	Results
83-5 Combined Chronic/Carcinogenic - Rat; Supplementary; 88/049; September 14, 1988	NOEL (females) = 8000 ppm (478 mg/kg/day) NOEL (males) > 12000 ppm (587 mg/kg/day) LEL (females) = 12000 ppm (757 mg/kg/day) Negative for carcinogenicity

Toxic Effects - Slightly decreased body weight in females at 12000 ppm.

Muta-Gene Mutation	
84-2 Ames; Acceptable; 84/0156; May 4, 1984	Negative
84-2 Reverse Mutation; Unacceptable; 88/0358; August 18, 1988	Inconclusive
84-2 CHO/HGPRT Forward Mutation; Unacceptable; 86/0214; July 18, 1986	Presumptively positive
Muta-Structural Chromosomal Aberration	
84-2 In Vitro Cytogenetics; Unacceptable; 86/0371; November 25, 1986	Inconclusive
84-2 In Vivo Cytogenetics; Acceptable; 88/1086; June 13, 1988	Negative
Muta-Other Genotoxic Effects	
84-2 Rec Assay; Unacceptable; 87/0025; October 16, 1986	Inconclusive
84-2 Micronucleus; Unacceptable; 86/0018; February 3, 1986	Inconclusive
84-2 UDS; Acceptable; 86/0135; June 1986	Negative
85-1 Metabolism - Rat; Acceptable; 86/5013; January 14, 1987	Metabolism is rapid

Study; Classification; Toxicity Category; Study Number; Date	Quinclorac, No. 325A Updated: October 1990
FACET® Herbicide 50% WP	Results
81-1 Acute Oral LD_{50} - Rat; Guideline; III; 86/0009; February 4, 1986	LD_{50} (M) = 3830 mg/kg (F) = 4070 mg/kg
81-2 Acute Dermal LD_{50} - Rat; Guideline; III; 86/0100; February 27, 1986	LD_{50} > 2000 mg/kg
81-3 Acute Inhalation LC_{50} - Rat; Guideline; III, 86/0291; April 23, 1986	LC_{t50} > 5.15 mg/L for t = 4 hrs
81-4 Primary Eye Irritation - Rabbit; Guideline; IV; 86/0102; January 17, 1986	Very mild irritation
81-5 Primary Dermal Irritation - Rabbit; Guideline; IV; 86/0101; February 28, 1986	Very slight dermal irritation
81-6 Dermal Sensitization - Guinea Pig; Minimum; 87/0013; April 4, 1987	Not a sensitizer

VI. DATA GAPS FOR TERRESTRIAL FOOD CROP USE

83-1 - Chronic Feeding - Rodent
83-2 - Carcinogenic - Rodent (1 Species)
83-3 - Developmental Toxicity (1 Species)
83-4 - Reproduction

VII. ACTION TAKEN TO REMOVE DATA GAPS AND OBTAIN ADDITIONAL INFORMATION

This is a "new chemical" and the first time that a terrestrial food crop usage has been requested. All available studies pertinent to the new usage have been submitted and evaluated. The data gaps have been identified in Section VI. DATA GAPS of this memorandum. Specific data deficiencies are identified in the Section XI. OTHER. The DERs are attached for further reference.

NOTE: It is recommended that this memorandum be submitted to the registrant in its entirety.

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VIII. REFERENCE DOSE (RfD)

The toxicological data base is currently inadequate for establishing permanent tolerances. Once sufficient data are obtained, the chemical will be referred to the RfD Committee for examination.

IX. PENDING REGULATORY ACTIONS

There are no pending regulatory actions against this pesticide at this time that TB-I is aware of.

X. TOXICOLOGICAL ISSUES

No other toxicological issues exist with the exception of the deficiencies noted in the submitted studies which are addressed in the DERs as well as in Section XI. OTHER.

XI. OTHER

A. The following studies must either be repeated, or additional information on the studies should be submitted as indicated below in an effort to upgrade the studies:

1. 83-1 - 2-Year Chronic/Carcinogenic - Rat (BASF No. 88/0409; September 14, 1988)

a. A rationale for selecting the doses used in the study should be submitted and it should be accompanied by the supporting data/studies.

b. The results of the histopathology examination must be validated for completeness and correctness of the diagnosis.

2. 83-3 - Developmental Toxicity - Rabbit (BASF No. 88/099; April 5, 1988)

a. Data to support the homogeneity and stability analysis of dosing solutions should be submitted.

b. Individual animal data for food and water consumption, number of corpora lutea, and fetal sex should be submitted.

3. 83-4 - 2-Generation Reproduction - Rat (BASF No. 88/0321; July 21, 1988)

a. Data on the stability analysis of the test material in the diet should be submitted.

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b. Individual animal data on food consumption with statistical analysis should be submitted.

4. 84-2 - Gene Mutation - S. typhimurium and E. coli (BASF No. 88/0358; August 18, 1988)

a. The use of an excessively high liver enzyme level in the S9 mix (30%) should be justified.

b. The results of the chemical analysis of test material solutions should be submitted.

5. Gene Mutation - CHO/HGPRT (BASF No. 86/0214; July 18, 1986)

a. The use of an excessively high liver enzyme level in the S9 mix (30%) should be justified.

b. Analytical data to support the actual test material concentrations in solution should be submitted.

c. A Quality Assurance Statement should be submitted.

In addition, the following two mutagenicity studies (translations required) should be submitted since they are reported to be weakly positive. These studies were referred to in the submission, but have not been submitted for evaluation.

a. Bericht Über die prüfung von Reg. No. 150 732, Charge N 55 im Ames-Test; 25.06.85 (85/233) BASF Aktiengesellschaft, Abt. Toxikologie, 6700 Ludwigschafen.

b. Bericht Über die Prüfung von Reg. No. 150 732, Charge N 57 im Ames-Test; 09.12.85 (85/448) BASF Aktiengesellschaft, Abt. Toxikologie, 6700 Ludwigschafen.

B. The following studies were reviewed for this action but not summarized in the TOX Profiles IV.

Technical Quinclorac	Results
81-1 Acute Oral LD_{50} - Rat; Guideline; III; 88/0171; June 1, 1988	LD_{50} > 2610 mg/kg
81-1 Acute Oral LD_{50} - Mouse; Guideline; IV; 86/0401; December 15, 1986	LD_{50} > 5000 mg/kg

Technical Quinclorac	Results
82-1 90-Day Subchronic Oral - Mouse; Supplementary; 88/0337;April 25, 1986	NOEL < 4000 ppm (M = 1000 mg/kg/day; F = 1467 mg/kg/day) LEL = 4000 ppm (M = 1000 mg/kg/day; F = 1467 mg/kg/day) (Based on decreased body weight gain in males and females)
82-1 90-Day Subchronic Oral - Mouse; Supplementary; 88/0338; August 11, 1988	NOEL > 500 ppm (75 mg/kg/day) (HDT)
Acute Intraperitoneal LD_{50} - Rat; Supplementary; 88/0242; December 12, 1983	LD_{50} = 681 mg/kg
4-Week Range Finding - Mouse; Supplementary; 86/0056; March 18, 1986	NOEL = 8000 ppm (1200 mg/kg/day) LEL = 16000 ppm (2400 mg/kg/day)

Toxic Effects - Increased SGPT, focal subacute interstitial inflammation, focal fatty infiltration and bile duct proliferation in the liver.

4-Week Range Finding - Rat; Supplementary; 85/0282; August 23, 1985	NOEL > 6400 ppm (960 mg/kg/day) (HDT)
4-Week Range Finding - Rat; Supplementary; 85/0284; August 23, 1985	NOEL > 15000 ppm (2250 mg/kg/day)

Toxic Effects - At 15000 ppm, there was a slight decrease in body weight, the rats appeared to be in poor shape with ruffled fur with "tubulopathy" of the kidneys.

4-Week Range Finding - Dog; Supplementary; 85/0234; November 18, 1983	NOEL = 3000 PPM (75 mg/kg/day) LEL = 9000 ppm (225 mg/kg/day)

Toxic Effects - Decrease in alkaline phosphatase at 9000 ppm. At 27000 there was decreased food consumption and body weight, vomiting, decreased in alkaline phosphatase, chronic focal or multifocal nephritis, decreased testes weight, focal dilation of kidney tubules with flattening of the epithelium and fatty degeneration of the glomeruli.

C. In a recent submission (PP#9G3797/FAP#9G03797; Project No. 0-1835; see memorandum of W. Greear dated September 10, 1990) BASF submitted additional information on three toxicity studies which was required for satisfying the toxicological data requirements for an EUP. The following information is presented in lieu of a supplemental DER.

Each study will be listed followed by 1) TB-I's initial comments specifying the deficiencies in the study, 2) BASF's response to the deficiencies, and 3) TB-I's conclusions as to the acceptability of the response and final assessment of the study.

Study #1: 83-3 Report on the Study to Determine the Prenatal Toxicity of Reg. No. 150 732 in Rats After Oral Administration (Gavage). Dr. J. Hellwig. May 12, 1987. BASF Reg. Doc. No. 87/0167. pp. 284. MRID No. 410635-24.

TB-I's Comments

Because of the absence of supporting data regarding the concentration and stability of dosing solutions, the NOEL and LEL could not be determined and the study is Core-Supplementary.

BASF's Response

An analytical report dated March 13, 1985 signed by Pawliczek indicates that dosing solutions with target concentrations of 438, 2920, and 8760 mg/100 mL had mean values of "501, 2.919, and 8.761 percent" when analyzed 3 days after preparation. A second report for the period of March 12 to 15, 1985 gave mean values of 486.3, 2906.8, and 8526.5 mg/100 g for target concentrations of 488, 2920, and 8760 mg/100 mL. (The signature with date was illegible.)

TB-I's Conclusion

[TB-I believes that an error was made in the first analytical report in that the target concentration reported to be 438 mg/100 mL was probably 488 mg/100 mL as indicated by the mean analytical concentration of 0.501 percent.] The two reports adequately define the concentrations of the dosing solutions and indicate that the test substance in 0.5 percent carboxymethylcellulose is stable for at least 3 days. TB-I's concerns are satisfied.

The study is therefore upgraded to Core-Minimum. The NOEL and LEL are as follows:

NOEL (maternal toxicity) = 146 mg/kg
LEL (maternal toxicity) = 438 mg/kg (reduced food consumption; increased water intake and mortality)

NOEL (developmental toxicity) = 438 mg/kg (HDT)

Study #2: 84-2 Report on the Study of Reg. No. 150 732 in the AMES Test (Standard Plate Test with Salmonella typhimurium) dated May 4, 1984. Dr. rer. nat. J. Engelhardt. BASF Reg. Doc. No. 84/0156. pp 26. MRID No. 410635-27.

TB-I's Comment #1

The author should justify use of the high (30%) S9 concentration in the S9 mix or repeat the study with the recommended S9 concentration (4%).

BASF's Response

The high concentration of S9 in the S9 mix is in accordance with TOX Method No. 005 of the Ecological and Toxicological Association of the Dyestuffs manufacturing industry and has been in use at the testing laboratory for a decade. Studies conducted on pesticides using this protocol have been accepted worldwide and by EPA/TSCA/FIFRA. In addition, positive controls used in each study demonstrated that the concentration of S9 in the S9 mix is capable of activating promutagens.

TB-I's Comment #2

The purity of the test material was not provided. In addition, analytical data to support the actual concentration was not provided.

BASF's Response

The test material used was from batch N 32 which had a purity of 96.5 percent which was confirmed by reanalysis in 1989. No concentration control analyses are performed in in vitro short-term mutagenicity tests like the Ames test. Usually, cytotoxicity is used as a measure for sufficient exposure of the test system to the test material. Although, significant bacterio-toxicity was not demonstrated, there was reduced his- background growth without S9 mix in TA

1537 and with S9 mix in TA 100 indicating that borderline bacterio-toxicity was achieved. The stability of the test material in the test system environment (aqueous) and in the solvent (DMSO) was proved after 48 and 24 hours, respectively.

TB-I's Conclusion

The test material was stored at ambient conditions after receipt on October 13, 1989. When reanalyzed on December 13, 1989 the mean analytical concentration of the test material was 97.0 percent compared to a theoretical concentration of 96.5 percent.

The background growth was reduced with S9 mix in TA 100 when compared to the negative control (DMSO) with S9 mix. (The values obtained were 96 and 132 revertants per plate, respectively.) The his- background growth appeared to be comparable for the test material and negative control for TA 1537 without the S9 mix.

The concentration of the test material at 0.1 percent in DMSO was 100.5 to 101.2 percent of the theoretical concentration after 24 hours at room temperature. The concentration of the test material in aqueous solution at 23 °C for a period of 48 hours was 100.0 to 100.6 percent of the theoretical concentrations of 31.6 to 31.8 mg/L.

BASF's response is acceptable. The study is therefore upgraded to "Acceptable."

Study #3: 84-4 Report on the Evaluation of Reg. No. 150 732 (ZNT No. 84/150) In Vitro Rat Primary Hepatocyte Unscheduled DNA Assay, Maria A. Cifone, June 1986. BASF Reg. Doc. No. 86/0135. pp. 24. MRID No. 410635-31.

TB-I's Comment

The study is not fully acceptable because of the lack of information on the purity of the test material and supporting analytical data to confirm the actual concentration.

BASF's Response

The test material was from batch N 32 which had a purity of 96.5 percent which was confirmed by reanalysis in 1989. No concentration control analyses are performed in in vitro short-term tests like the UDS assay. Usually,

cytotoxicity is used as a measure for significant exposure to the test material. Cytotoxicity was clearly demonstrated which indicates that the cells were exposed to the test material. The stability of the test material in the test system environment (aqueous) and in the solvent (DMSO) was proved after 48 and 24 hours, respectively.

TB-I's Conclusion

The data provide by BASF is identical with that provided for the Ames test regarding the concentration and stability of the test material. Cytotoxicity was clearly demonstrated in the UDS assay.

BASF's response is acceptable. The study is therefore upgraded to "Acceptable."

Attachment

54689:I/C:WP50:Greear:C.Disk:KENCO:9/24/90:EK:VO:EK:VO:EK
R:55949:Greear:C.Disk:KENCO:10/12/90:EK

NOV 19 1990

Reviewed By: William B. Greear, M.P.H. William B. Greear 1/15/90
Review Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. M Copley 1/30/90
Review Section II, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: Guidelines Series 81-1 - Acute Oral Toxicity - Rat

TOX Chem No.: 325A
MRID No.: 410635-06

Test Material: Reg. No. 150-732/BAS 514..H (technical); purity not stated

Synonyms: 3,7-dichloro-8-quinolinecarboxylic acid, quinclorac

Sponsor: BASF Corporation Chemicals Division
Parsippany, NJ 07054

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
D-6700 Ludwigshafen/Rhein, FRG

Title of Report: Report on the Study of Acute Oral Toxicity in Rats of Reg. No. 150-732, BAS 514 H Dated December 12, 1983.

Author: O.J. Grundler

Study No.: 83/0240

Classification:

Guideline - Satisfies Guidelines Series 81-1 (Acute Oral Toxicity).

Conclusions:

LD_{50} (male) = 3060 mg/kg, slope = 1.28
LD_{50} (female) = 2190 mg/kg, slope = 2.13
LD_{50} (combined) = 2680 mg/kg, slope = 1.66

Toxicity Category: III

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Materials and Methods:

One hundred and twenty Wistar rats with group mean weights of 170 to 201 g (males) and 161 to 180 g (females) were obtained from K. Thomas GMBH, Biberach, FRG, and allowed to acclimate to laboratory conditions for at least 1 week. The rats were housed five per cage in stainless steel mesh cages in air-conditioned rooms with a temperature of 20 to 24 °C, relative humidity of 30 to 70 percent and a 12-hour on/12-hour off light cycle, Kliba-Labordiaet and tap water were available ad libitum except that food was withheld 16 hours prior to dosing. The rats were administered 562, 825, 1210, 1780, and 2610 mg/kg of the test material in 0.5 percent aqueous carboxymethyl cellulose by gavage at a constant volume of 10 mL/kg. The rats were observed for clinical signs of mortality at several times on the day of dosing and at least once on workdays and once on holidays for a period of 14 days. Body weights were determined on days 2, 3, 4, 7, and 13. All animals were necropsied. The LD_{50} was calculated using Finney's probit analysis. Quality assurance inspections were not conducted. The study was not conducted under GLP conditions.

Results:

The following table provides information on the dose levels at which mortality occurred:

Dose mg/kg	Number Dead/Number Treated	
	Male	Female
562	0/10	0/10
825	0/10	2/10
1210	0/10	2/10
1780	0/10	3/10
2610	3/10	6/10
3830	8/10	8/10

Deaths usually occurred between days 2 to 7. Males and females exhibited dyspnea, apathy, staggering, spastic gait, piloerection, exsiccosis (dehydration), and poor general state. The clinical signs were present in males during the first 3 days in the top three dose levels. The signs were present in females during the first 9 days in all groups except the low-dose group. The mean body weight of surviving males appeared to decrease with increasing dose level. The mean body weights of females were similar in all treated groups. Rats that died during the study exhibited ulcerations in the glandular stomach, full stomachs, hematinized contents of the intestines, and atonic intestines. Surviving rats had no gross abnormalities.

Reviewed By. William B. Greear, M.P.H. William B. Greear 1/5/90
Review Section II, Toxicology Branch I - IRS (H75090)
Secondary Reviewer: Marion P. Copley, D.V.M. Marion P. Copley 1/30/90
Review Section II, Toxicology Branch I - IRS (H75090)

DATA EVALUATION REPORT

Study Type: Guidelines Series 81-1 - Acute Oral Toxicity - Rat

TOX Chem No.: 335A
MRID No.: 410635-05

Test Material: Reg. No. 150-732/BAS 514..H (pure ai)

Synonyms: 3,7-dichloro-8-quinolinecarboxylic acid, quinclorac

Sponsor: BASF Corporation Chemicals Division
Parsippany, NJ 07054

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
D-6700 Ludwigshafen/Rhein, W. Germany

Title of Report: Report on the Study of the Acute Oral Toxicity in Rats of Reg. No. 150-732, Dated June 1, 1988.

Author: O.J. Grundler

Study No.: 88/0171

Classification:

Guideline - Satisfies Guidelines Series 81-1 (Acute Oral Toxicity).

Conclusion: LD_{50} > 2610 mg/kg

Toxicity Category: III

21

Materials and Methods:

Forty Wistar rats with an age of 12 weeks and with group mean weights of 160 to 170 g (male) and 170 g (female) were obtained from K. Thomas, GMBH, Biberach, FRG, and were allowed to acclimate to laboratory conditions for at least 1 week. The rats were housed five per cage in stainless steel wire mesh cages in a room with temperature of 20 to 26 °C, relative humidity of 45 to 75 percent, and 12-hour on/12-hour off light cycle. There were also 15 to 20 air changes per hour. Food and water were available ad libitum except that food was withdrawn 16 hours prior to dosing. The rats were administered 825, 1210, 1780, and 2610 mg/kg of the test material in 0.5 percent aqueous carboxymethyl cellulose by gavage at a constant volume of 10 mL/kg. The rats were observed for clinical signs of toxicity and mortality at several times on the day of dosing and once every workday and once on holidays for a period of 14 days. Body weights were determined on days 2, 7, and 13. All animals were necropsied. Quality assurance inspections were not conducted. The study was not conducted under GLP conditions.

Results:

The following table provides information on the dose levels at which mortality occurred:

Dose mg/kg	Number Dead/Number Treated	
	Male	Female
825	0/5	0/5
1210	0/5	0/5
1780	0/5	1/5
2610	1/5	1/5

Deaths occurred between days 1 to 7. Males and females in the two highest dose levels exhibited dyspnea, apathy, staggering, spastic gate, ruffled fur, diarrhea, cachexia, and a poor general state from 4 hours to day 5. Mean body weight gains were comparable among all surviving rats. Rats that died had congestion of the lungs. All surviving rats showed no gross abnormalities.

Reviewed By: William H. Greear, M.P.H. William B. Greear 1/5/90
Review Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. MCopley 1/30/90
Review Section II, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: Guidelines Series 81-1 - Acute Oral Toxicity - Mouse

TOX Chem No.: 325A
MRID No.: 410635-07

Test Material: Reg. No. 150-732/BAS 514..H (technical); purity 98.29%

Synonyms: 3,7-dichloro-8-quinolinecarboxylic acid, quinclorac

Sponsor: BASF Corporation Chemicals Division
Parsippany, NY

Testing Facility: BASF Aktiengeselschaft
Department of Toxicology
D-6700 Ludwigshafen/Rhein, FRG

Title of Report: Report on the Study of Acute Toxicity on the Mouse Based on OECD and EPA (FIFRA) of Reg. No. 150-732.

Author: H. Kieczka

Study No./Date: 86/0491 - December 15, 1986

Classification:

Guideline - Satisfies Guideline Series 81-1 (Acute Oral Toxicity).

Conclusions: LD_{50} > 5000 mg/kg

Toxicity Category: IV

23

Materials and Methods:

Forty B6C3F1 mice with mean weights of 19.0 to 20.0 g (male) and 17.0 to 18.0 g (female) were obtained from Charles River Breeding Laboratory, Wilmington, MA, and were allowed to acclimate to laboratory conditions for at least 1 week. The mice were housed 5 per cage in Makrolan cages in a room with temperature of 20 to 24 °C, relative humidity of 30 to 70 percent, and a 12-hour on/12-hour off light cycle. Kliba-Labordiaet and tap water were available ad libitum except that food was withheld for a period of 16 hours prior to dosing. The mice were administered 200, 600, 2000, and 5000 mg/kg of the test material in 0.5 percent carboxymethyl cellulose by gavage at a constant volume of 10 mL/kg. The mice were observed for clinical signs of toxicity and mortality at several times on the day of dosing and at least once each workday and once on holidays for a 14-day period. Body weights were determined on days 7 and 13. All animals were necropsied. Quality assurance inspections were made at several intervals and a QAU statement was signed and dated December 15, 1986. The study was not conducted under GLP conditions.

Results:

The following table provides information on the dose levels at which mortality occurred:

Dose mg/kg	Number Dead/Number Treated	
	Male	Female
200	0/5	0/5
600	1/5	0/5
2000	0/5	0/5
5000	2/5	1/5

Deaths occurred between days 1 to 7. Males and females in the top two dose levels exhibited dyspnea, apathy, staggering, piloerection, and a poor general state from 4 hours to day 6. Mean body weights were comparable among all surviving mice. Mice that died during the study showed general congestive hyperemia. The surviving mice had no gross abnormalities.

24

Reviewed By: William B. Greear, M.P.H. William B. Greear 1/5/90
Review Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. MPCopley 1/30/90
Review Section II, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: Guidelines Series 81-2 - Acute Dermal Toxicity Rat

TOX Chem No.: 325A
MRID No.: 410635-00

Test Material: Req. No. 150-732/BAS 514..H (technical); purity not stated

Synonyms: 3,7-dichloro-8-quinolinecarboxylic acid, quinclorac

Sponsor: BASF Corporation Chemicals Division
Parsippany, NJ 07054

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
D-6700 Ludwigshafen/Rhein, FRG

Title of Report: Report on the Study of the Acute Dermal Toxicity in Rats of Req. No. 150-732, BAS 514 H Dated December 12, 1989.

Author: D.I. Grundler

Study No.: 89-0244

Classification:

Guideline - Satisfies Guidelines Series 81-2 (Acute Dermal Toxicity).

Conclusions: LD_{50} > 2000 mg/kg

Toxicity Category: III

25

Materials and Methods:

Ten male and ten female Wistar rats with mean body weights of 240 and 216 g, respectively, were obtained from C. Thomas [illegible], Biotech, FRG, and allowed to acclimate to laboratory conditions for at least 1 week. The rats were individually housed in stainless steel wire mesh cages in a room with temperatures of 20 to 24 °C, relative humidity of 30 to 70 percent, and a 12-hour on/12-hour off light cycle. Ssniba-Laboratiaet and tap water were available ad libitum. At least 15 hours prior to application of the test material at a dose level of 2000 mg/kg, dorsal and dorsolateral parts of the trunk of the rats were clipped free of fur. The test sites were covered with a semiocclusive dressing for 24 hours. After removal of the dressing, the test sites were rinsed with warm water. The rats were observed for clinical signs of toxicity and mortality several times on the day of dosing and at least once each workday and once on holidays for a period of 15 days. Irritation of the skin was scored after 30 to 60 minutes of removal of the dressings and at weekly intervals thereafter. Body weights were determined on days 2, 7, and 15. All animals received a gross necropsy. Quality assurance inspections were not conducted. The study was not conducted under GLP conditions.

Results:

No deaths occurred, no clinical signs of toxicity were observed, and no skin irritation was present. Mean body weights were reduced on day 2, but the rats retained the weight lost by day 7. No gross abnormalities were noted in the survivors at necropsy.

Reviewed By: William B. Greear, M.P.H. William B. Greear 1/30/90
Review Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. M Copley 1/30/90
Review Section II, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: Guidelines Series 81-3 - Acute Inhalation Toxicity - Rat

TOX Chem No.: 325A
MRID No.: 410635-10

Test Material: Reg. No. 150-732/BAS 514..H (technical); purity not stated

Synonyms: 3,7-dichloro-8-quinolinecarboxylic acid, quinclorac

Sponsor: BASF Corporation Chemicals Division
Parsippany, NJ 07054

Testing Facility: BASF Aktiengesellschaft
Department of Toxicity
D-6700 Ludwigshafen, FRG

Title of Report: Report on the Study of Acute Inhalation Toxicity LC_{50} 4 Hours (Rat) of Reg. No. 150-732 Dust/Aerosol Study.

Author: H.J. Klimisch

Study No./Date: 85/0271 - August 20, 1985

Classification:

Minimum Data - Satisfies Guidelines Series 81-3 (Acute Inhalation Toxicity).

Conclusions: LC_{50} > 5.2 mg/L for t = 4 hours

Toxicity Category: III

Justification of Classification:

The analytical concentration was not determined.

27

Materials and Methods:

Ten male and ten female 8-week-old rats with body weights of 243 ± 15 g and 170 ± 14 g, respectively, were obtained from K. Thomas GMBH, Biberach, FRG. The rats were maintained in a room with temperature of 20 to 24 °C, relative humidity of 30 to 70 percent, and 12-hour on/12-hour off light cycle. The rats were housed five per cage in Becker type D III cages. Kliba rat/mouse laboratory diet and water were available ad libitum during the postexposure period. The exposure system was a head-nose inhalation system INA 20 (glass-steel construction). The dust air mixture was generated with vibration dust partitioning equipment. The concentration was adjusted by varying the aperture width and by varying the amplitude of the oscillations of the metering breaker. The air flow was set at 1500 L/hour compressed air by the injector and 1500 L/hour conditioned air as dilution air. The exposure was 4 hours in duration. The concentration was determined gravimetrically by drawing the dust aerosol through a preweighed filter. Particle size analysis was conducted 30 minutes after beginning the exposure using an Anderson Stack Sampler Mark III (cascade impactor). The animals were observed for a 14-day period. Body weights were determined initially and on days 7 and 14. All animals received a gross necropsy. A historical control was used in analyzing the results of the study. Quality assurance inspections were not conducted. The study was not conducted under GLP conditions.

Results:

No deaths occurred and no clinical signs of toxicity were observed. Body weight gain of treated rats was similar to the historical control group. No abnormalities were noted at necropsy. The nominal concentration was determined to be 15.25 mg/L. The mass median aerodynamic diameter (MMAD) was 2.3 micrometers and the geometric standard deviation was 3.2.

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Reviewed By: William R. Greear, M.P.H. William R. Greear 1/5/90
Review Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. M Copley 1/30/90
Review Section II, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: Guidelines Series 81-4 - Primary Eye Irritation - Rabbit

TOX Chem No.: 335A
MRID No.: 410635-11

Test Material: Reg. No. 150-732/BAS 514..H (technical); purity not stated

Synonyms: 3,7-dichloro-8-quinolinecarboxylic acid, quinclorac

Sponsor: BASF Corporation Chemicals Division
Parsippany, NJ 07054

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
D-6700 Ludwigshafen/Rhein, FRG

Title of Report: Report on the Study of the Irritation to the Eye of the White Rabbit Based on Draize of Test No. 150-732, BAS 514 H Dated August 18, 1988.

Author: O.J. Grundler

Study No.: 83/0171

Classification:

Guideline - Satisfies Guidelines Series 81-4 (Primary Eye Irritation).

Conclusions: Mild irritant reversible by day 8.

Toxicity Category: III

29 2

Materials and Methods:

Six (2 male, 4 female) White Vienna rabbits were obtained from Gaukler, Main, FRG, and were acclimated for at least 8 days to laboratory conditions. The rabbits were individually housed in cages made of stainless steel with wire mesh walk floors in a room with temperature of 20 to 24 °C, relative humidity of 30 to 70 percent, and a 12-hour on/12-hour off light cycle. Ovator Solikanin (diet) was fed to the animals at about 130 g per day with 250 mL of tap water. One-tenth mL (approximately 38 mg) of the dry test substance was placed in the conjunctival sac of the right eye of each rabbit. Ocular readings for irritation were made at 1, 24, 48, and 72 hours, and at 8 and 15 days. Quality assurance inspections were not conducted. The study was not conducted under GLP conditions.

Results:

There was redness, chemosis, and discharge of the conjunctivae (grades 1 and 2) at 1 hour. At 48 hours, only grades 1 and 2 redness of the conjunctivae persisted. All eyes were normal by day 8.

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Reviewed By: William B. Greear, M.P.H. William B. Greear 1/5/90
Review Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. M Copley 1/30/90
Review Section II, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: Guidelines Series 81-5 - Primary Dermal Irritation - Rabbit

TOX Chem No.: 325A
MRID No.: 410635-12

Test Material: Reg. No. 150-732/BAS 514..H (technical); purity not stated

Synonyms: 3,7-dichloro-8-quinolinecarboxylic acid, quinclorac

Sponsor: BASF Corporation Chemicals Division
Parsippany, NJ

Testing Facility: BASF Aktiengesellschaft
Department of Toxicity
D-6700 Ludwigshafen/Rhein, FRG

Title of Report: Report on the Study of the Irritation to the Intact and Abraded Dorsal Skin of the White Rabbit Based on Draize of Reg. No. 150-732; BAS 514 H Dated August 18, 1983.

Author: D.J. Grundler

Study No.: 83/0168

Classification:

Guideline - Satisfies Guidelines Series 81-5 - (Primary Dermal Irritation).

Conclusions: Not an irritant.

Toxicity Category: IV

31

Materials and Methods:

Six (3 male, 3 female) White Vienna rabbits were obtained from Gaukler, Main, FRG, and allowed to acclimate to laboratory conditions for at least 9 days. The rabbits were individually housed in cages made of stainless steel with wire mesh walk floors in a room with temperature of 20 to 24 °C, relative humidity of 30 to 70 percent, and a 12-hour on/12-hour off light cycle. Ovator Solikanin (diet) was fed to the rabbits at about 130 g per day with 250 mL of tap water. The fur was clipped from the skin on the upper third of the back or flank of each rabbit at least 15 hours prior to application of the test material as a 50% w/w aqueous formulation. The formulation (approximately 0.5 g of test material) was placed on a 2.5 x 2.5 cm^2 area on contact and abraded skin and left in place for 24 hours under occlusive dressing. After removal of the dressing the remaining test material was wiped off. The test sites were scored 30 to 60 minutes, 48 and 78 hours, and 9 and 15 days after removal of the dressing. Quality assurance inspections were not conducted. The study was not conducted under GLP conditions.

Results: No irritation was produced.

Reviewed By: William B. Greear, M.P.H. William B. Greear 1/5/90
Review Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. M Copley 1/30/90
Review Section II, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: Acute Intraperitoneal Toxicity - Rat

TOX Chem No.: 325A
MRID No.: 410635-09

Test Material: Reg. No. 150-732/BAS 514..H (technical); purity not stated

Synonyms: 3,7-dichloro-8-quinolinecarboxylic acid, quinclorac

Sponsor: BASF Corporation Chemicals Division
Parsippany, NJ 07054

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
D-6700 Ludwigshafen/Rhein, FRG

Title of Report: Report on the Acute Intraperitoneal Toxicity in Rats of Reg. No. 150-732 (BAS 514 H) Dated December 12, 1983.

Author: O.J. Grundler

Study No.: 83/0242

Classification: Supplementary

Conclusions: LD_{50} = 681 mg/kg, slope = 1.12

93

Materials and Methods:

One hundred and twenty Wistar rats with mean group weights of 179 to 217 g (male) and 160 to 179 g (female) were obtained from K. Thomas GMBH, Biberach, FRG, and allowed to acclimate to laboratory conditions for at least 1 week. The rats were housed five per cage in stainless steel wire mesh cages in a room with a temperature of 20 to 24 °C, relative humidity of 30 to 70 percent, and a 12-hour on/12-hour off light cycle. Kliba-Labordiaet and tap water were available ad libitum except that food was withheld 16 hours prior to dosing. The rats were administered 215, 383, 562, 825, 1210, and 2000 mg/kg of the test material in 0.5 percent carboxymethyl cellulose at a constant volume of 10 mL/kg by intraperitoneal injection. The rats were examined for clinical signs of toxicity and mortality at several times on the day of dosing and once on each workday and once on holidays for a period of 14 days. Body weights were determined on days 0, 3, 7, and 14. All animals were necropsied. Quality assurance inspections were not conducted. The study was not conducted under GLP conditions.

Results:

The following table provides information on the dose levels at which mortality occurred:

Dose mg/kg	Number Dead/Number Treated	
	Male	Female
215	0/10	0/10
383	0/10	2/10
562	1/10	1/10
825	8/10	10/10
1210	10/10	10/10
2000	10/10	10/10

Deaths occurred from 1 hour to 7 days. Males exhibited dyspnea, apathy, staggering, tremors, piloerection, diarrhea, exsiccosis (dehydration), and a poor general state from 15 minutes to 6 days. Females exhibited dyspnea, apathy, staggering, piloerection, and a poor general state from 15 minutes to 6 days. Mean body weights of survivors were comparable among the treatment groups. Animals that died during the study exhibited general congestive hyperemia, bloody ulceration of the glandular stomach and milky-white liquid in the stomach. Surviving animals exhibited fusions of the stomach with the liver, milky coating of the surface of the liver and spleen and thickened walls of the liver.

Reviewed By: William B. Greear, M.P.H. 10/10/90
Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section II, Toxicology Branch I - IRS (H7509C)
10/23/90

DATA EVALUATION REPORT

Study Type: Guideline Series 82-1
3-Month Feeding - Rat*

TOX Chem No.: 325A

Test Material: Reg. No. 150 732

MRID No.: 410635-16

Synonyms: BAS 514..H, Quinclorac

Study Number: BASF 88/5145

Sponsor: BASF

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
D-6700 Lugwigshafen, FRG

Title of Report: Report on the Study of the Subchronic Toxicity of Reg. No. 150 732 in Rats After 3 Months Administration in the Diet.

Author: B. Kuhborth

Report Issued: March 13, 1986

Conclusions:

NOEL = 4000 ppm (M - 302.3 and F - 358.0 mg/kg/day)

LEL = 12,000 ppm (M - 929.9 and F - 1035.4 mg/kg/day) based on decreases in body weight gain, food consumption and an increase in water intake in males and females, and decrease in monocytes in females, increases in SGOT and SGPT in males, and pathological changes in the kidneys of males (slight to minimal focal chronic interstitial nephritis).

The sponsor should define the measurement microkatal/liter.

Classification: Core-Supplementary

The study does not satisfy the requirement for a Guideline Series 82-1 90-day feeding study in rodents.

* incl. summary of range finding [illegible]

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Justification of Classification:

Analysis of the purity of the test material was not provided. The stability and homogeneity of the test substance in the diet were not provided.

A. Materials:

1. Test Compound - Reg. No. 150 732; Description - not reported; Batch No. N32; Purity 96.5%.

2. Test Animals - Species: Rat; Strain: Wistar Chbb-THOM(SPF), Age: 42 days; Weight: Male 160.4 (151-172) g, Female 126.0 (115-134) g; Source: Karl Thomae GmbH, Biberach/Riss, FRG.

B. Study Design:

1. Animal Assignment - Animals were assigned to the following test groups:

Test Group	Dose in Diet (ppm)	Main Study Months Male	Female
1 Control	0	10	10
2 Low (LDT)	1000	10	10
3 Mid (MDT)	4000	10	10
4 High (HDT)	12000	10	10

The rats were singly housed in DK III-type stainless steel wire mesh cages on racks in a room with temperature of 20 to 24 degrees C, relative humidity of 30 to 70 percent, and a 12-hour-on/12-hour-off light cycle.

2. Diet Preparation - Diet was prepared every 4 weeks. The test material was analyzed for the percent ai and the impurities were determined. The stability and homogeneity of the test substance were proven analytically. The stability of the test substance in the diet was previously demonstrated for a period of 30 days. The homogeneity of the test diets were proven analytically. A premix was made by mixing the test material with a small amount of the feed. This premix was then mixed with the appropriate amount of feed to achieve the appropriate test diets. Two samples of each test diet were analyzed at the beginning of the study and after 8 weeks. The method of analysis used was HPLC.

Results - The analyses of the purity of the test material and its contaminants were not provided. Neither the homogeneity nor stability of the test diets were provided in this report. At the initiation of the study, mean values of 1044, 4524, and 11,144 mg/kg were obtained for the 1000, 4000, and 12,000 ppm groups, respectively. After 8 weeks, mean values of 970, 3604, and 12,199 mg/kg were obtained for the 1000, 4000, and 12,000 ppm groups, respectively.

3. Animals received food (Kliba 343 rat/mouse/hamster maintenance diet) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: ANOVA, Dunnett's test, and a t-test generalized by Williams.

5. Quality assurance was conducted on May 18, August 10, August 27, September 12, 1984 and on January 10, 1986.

C. Methods and Results:

1. Observations - Animals were inspected daily for signs of toxicity and twice daily for mortality. At each weighing, the animals were examined and palpitated for masses.

Results - Toxicity - No compound-related clinical signs of toxicity were observed.

Mortality (Survival) - No deaths occurred.

2. Body Weight - Animals were weighed once weekly for 3 months.

Results - Body weight gain was decreased by 9.2 and 13.0 percent in males and females in the 12,000 ppm group, respectively, when compared to controls over the 91-day period (see Table 1 below - reviewer calculated).

Table 1. Body Weight Gain (g) and Percent Gain Relative to Controls

Group (ppm)	Interval (Days)			
Males	0 to 28	28 to 63	63 to 91	0 to 91
0	162.3	105.1	31.3	298.7
1000	170.0 (4.7)*	108.7 (3.4)	37.9 (3.9)	316.6 (6.0)
4000	166.0 (2.3)	109.6 (4.3)	40.6 (29.7)	316.2 (5.9)
12000	143.7 (-11.5)	93.3 (-11.2)	34.1 (3.5)	271.1 (-9.2)
Females				
0	73.9	37.4	14.9	126.2
1000	71.5 (-3.2)	45.0 (20.3)	17.3 (16.1)	133.8 (6.0)
4000	65.3 (41.6)	44.5 (19.0)	11.6 (-22.1)	121.4 (-3.8)
12000	60.0 (-18.8)	39.6 (5.9)	10.2 (-31.5)	109.8 (-13.0)

*Body weight gain (percent gain relative to controls).

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3. Food Consumption, Water Intake, and Compound Intake - Consumption was determined and mean daily diet consumption was calculated. Compound intake was calculated from the consumption and body weight gain data.

Results - Food consumption was marginally decreased in the 12,000 ppm group (up to 9%) on several days during the study (see Table 2 below - reviewer calculated).

Table 2. Food Consumption (g/mg bwt/day) Percent Relative to Control Group (ppm)

Group (ppm)	Day			
Males	7	28	61	91
0	112	83.7	64.1	55.4
1000	113 (0.9)*	81.9 (-2.2)	61.2 (-4.5)	54.2 (-2.2)
4000	109 (-2.7)	81.0 (-3.2)	61.4 (-4.2)	53.2 (-4.0)
12000	102 (-8.9)	83.7 (0)	63.3 (-1.2)	54.5 (-1.6)
Females				
0	115	87.4	75.8	68.9
1000	116 (0.9)	08.1 (0.8)	78.4 (3.4)	69.7 (1.2)
4000	116 (0.9)	91.3 (4.5)	78.4 (3.4)	72.3 (4.9)
12000	109 (-5.2)	89.4 (2.3)	75.0 (-1.1)	68.4 (-0.7)

*g/kg/day (percent relative to controls).

Food Efficiency - Not reported.

Compound Intake - Mean compound intake in males in the 1000, 4000, and 12,000 ppm groups was 76.8 mg/kg/day, 302.3 mg/kg/day and 929.9 mg/kg/day, respectively. Mean compound intake in females in the 1000, 4000, and 12,000 ppm groups was 86.7 mg/kg/day, 358.0 mg/kg/day, and 1035.4 mg/kg/day, respectively.

Water Intake was significantly increased in male rats in the 12,000 ppm group between 10 and 41 percent and in females in the 12,000 ppm group between 5 and 43 percent (see Table 3 below - not statistically analyzed).

Table 3. Water Intake (g/Day)

Group (ppm)	Day				
Males	15 to 16	35 to 36	56 to 57	77 to 78	87 to 88
0	27.20	28.70	31.20	25.78	27.30
1000	27.30	29.50	25.80	24.90	29.30
4000	27.40	24.67	28.90	27.40	29.70
12000	36.33	31.50	37.38	31.80	34.30
Females					
0	18.60	18.60	21.44	20.50	23.80
1000	15.90	18.00	20.70	21.20	21.90
4000	15.22	18.30	21.60	21.60	24.60
12000	19.50	22.20	24.00	25.90	32.00

4. Ophthalmological Examinations were performed initially and at termination on animals in the control and 12,000 ppm groups.

   Results - Unremarkable.

5. Blood was collected at 86 days for hematology and clinical analysis from 10 animals/sex group. The CHECKED (X) parameters were examined.

   a. Hematology

X		X	
X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HCS)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)	X	Mean corpuscular volume (MCV)
X	Platelet count	X	Reticulocyte count
X	Prothrombin time		

   Results - Males in the 12,000 ppm group exhibited a statistically significant decrease in the hematocrit. Females in the 12,000 ppm group exhibited a statistically significant decrease in the hematocrit, hemoglobin and MCH values (see Table 4 below).

Table 4. Hematology Parameters

Group	RBC $10^{12}/l$	HCT (%)	HGB (mmol/l)	MCH (fmol)	MCV (fl)	MCHC (mmol/l)
Males						
0	8.34	41	9.25	1.12	49.19	22.88
1000	8.36	41	8.92	1.13	48.61	23.07
4000	8.17	40	9.03	1.11	48.88	22.61
12000	8.07	39*	9.04	1.11	48.26	22.81
Females						
0	8.15	40	9.29	1.14	49.63	22.96
1000	8.12	40	9.22	1.14	49.46	22.95
4000	7.99	39	9.20	1.13	49.36	22.96
12000	7.62	37*	8.45*	1.11**	49.01	22.62

* $p < 0.05$
** $p < 0.01$

In addition, there were statistically significant increases in the monocytes and neutrophilic segmented granulocytes and a decrease in lymphocytes in females in the 12,000 ppm group. The percent of monocytes was 5.70, 6.80, and 7.40 and 9.50 percent in the 0, 1000, 4000, and 12,000 ppm groups, respectively. The percent of neutrophilic segmented granulocytes was 10.90, 16.50, 13.90, and 19.80 percent in the 0, 1000, 4000, and 12,000 ppm groups, respectively. The percent of lymphocytes was 81.10, 74.80, 77.20, and 68.80 percent in the 0, 1000, 4000, and 12,000 ppm groups, respectively.

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b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
X	Calcium*		Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorus*	X	Cholesterol*
X	Potassium*		Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total bilirubin*
X	Alkaline phosphatase (ALK)	X	Total serum protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatinine phosphokinase*		Serum protein electrophoresis
	Lactic acid dehydrogenase (LAD)		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		

*Required for subchronic and chronic studies.

Results - SGOT and SGPT were significantly (statistically) increased in males in the 12,000 ppm group. Values for SGOT were 1.488, 1.939, 2.092, and 2.200 ukat/l in the 0, 1000, 4000, and 12,000 ppm groups, respectively. Values for SGPT were 0.832, 0.883, 0.973, and 1.050 ukat/l* in the 0, 1000, 4000, and 12,000 ppm groups, respectively.

6. Urinalysis - Urine was collected from animals at 80 days. The CHECKED (X) parameters were examined.

X		X	
	Appearance	X	Glucose
	Volume	X	Ketones
	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)	X	Nitrite
X	Protein	X	Urobilinogen

Results - Unremarkable.

7. Sacrifice and Pathology - All animals that died and that were sacrificed on schedule were subject to gross

*Microkatal/liter should be defined by the sponsor.

pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	X	Aorta*	X	Brain*
	Salivary glands*	X	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*		Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen		Eyes (optic nerve)*
X	Jejunum*	X	Thymus*		Glandular
X	Ileum*		Urogenital	XX	Adrenal gland*
X	Cecum*	XX	Kidneys*		Lacrimal gland
X	Colon*	X	Urinary bladder*		Mammary gland*
X	Rectum*	XX	Testes*		Parathyroids*
XX	Liver*		Epididymides	X	Thyroids*
	Gall bladder*		Prostate		Other
X	Pancreas*		Seminal vesicle	X	Bone*
	Respiratory	X	Ovaries*		Skeletal muscle*
X	Trachea*	X	Uterus*		Skin*
X	Lung*			X	All gross lesions and masses*

*Required for subchronic and chronic studies.

Histological examination of all tissues indicated above was conducted on controls and animals in the 12,000 ppm group. Only the lungs, liver, and kidneys and all gross lesions were examined in the 1000 and 4000 ppm groups.

Results

a. Organ Weight - Unremarkable.

b. Gross Pathology - Two of 10 males in the 12,000 ppm groups exhibited small cortical scars in the kidney.

c. Microscopic Pathology - Minimal to slight focal chronic interstitial nephritis occurred in four males and one female in the 12,000 ppm group and in one male and one female in the 1000 ppm group. This lesion was not found in the control and 4000 ppm groups. This lesion appears to be compound-related in males in the 12,000 ppm group.

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D. Discussion:

No clinical signs of toxicity were observed and no deaths occurred. Body weight gain was slightly decreased in males (9%) and females (13%) in the 12,000 ppm group. Water intake was significantly increased in males (10 to 41%) and females (5 to 43%) in the 12,000 ppm group. Although males in the 12,000 ppm group had a decrease in HCT and females in the 12,000 ppm group exhibited decreases in HCT, HGB, and MCH, these changes were not biologically significant. There were increases in monocytes and neutrophilic segmented granulocytes and a decrease in lymphocytes in females in the 12,000 ppm group on analysis of the differential leukocyte count. However, only the increase in monocytes appears to be dose-related and biologically significant in the 12,000 ppm group. SGOT and SGPT were significantly increased in males in the 12,000 ppm group. Two males in the 12,000 ppm group exhibited gross kidney lesions (cortical scars). In addition, on histological examination 4 of 10 males in the 12,000 ppm group had minimal to slight focal chronic interstitial nephritis compared with 0/10 in the controls. The increase in water intake and the appearance of kidney lesions are probably related, indicating that the kidney is a target organ.

[In a 4-week range-finding study #85/0284, the kidney exhibited lesions at 1500 and 3000 mg/kg/day.]

The following range-finding studies were examined and conclusions drawn. DERs will not be completed for these studies.

Title: Report on the Study of the Toxicity of Reg. No. 150 732 in Rats After 4 Weeks Administration in the Diet (1st Range-Finding Study) (BASF #85/0282; 8/23/85) - MRID No. 410635-14.

Summary - No adverse affects were observed.

NOEL > 6400 ppm (640 mg/kg/day)

Core-Supplementary

Title: Report on the Study of the Toxicity of Reg. No. 150 732 in Rats After 4 Weeks Administration in the Diet (2nd Range-Finding Study) (BASF #85/0284; 8/23/85) - MRID No. 410635-15.

Summary - The test material was fed to Wistar Chbb-THOM (SPF) rats at 0, 15,000, and 30,000 ppm in the diet for 4 weeks. At 15,000 ppm, there was a slight decrease in body weight, the animals appeared to be in a poor general condition with ruffled fur, and there was "tubulopathy" of the kidneys. At 30,000 ppm, the animals exhibited decreased food consumption and body weight, a poor condition with ruffled fur, increased bilirubin, creatinine, urea, potassium, SGPT, SGOT, and albumin, decreased sodium chloride, and alkaline phosphatase, increase in neutrophilic segmented granulocytes in males, cachexia and exsiccosis, decreased testes and liver weight, a fine granular structure of the kidneys with white stipples, "tubulopathy" of the kidney, tubular atrophy of the testes, lymphocytes depletion of the spleen, cloudy swelling of hepatocytes, and vacuolization of the adrenal cortical cells. One male died during the study.

NOEL < 15,000 ppm (1500 mg/kg/day)

Core-Supplementary

NOV 19 1990

Reviewed By: William B. Greear, M.P.H. William B. Greear 10/16/90
Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section II, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: Guideline Series 82-1 3-Month 1/ Feeding - Mouse* TOX Chem No.: 325A

Test Material: Reg. No. 150 732 MRID No.: 410635-18

Synonyms: BAS 514..H, quinclorac

Study Number: BASF 88/0337

Sponsor: BASF

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
6700 Lugwigshafen, FRG

Title of Report: Report on the Study of the Oral Toxicity of Reg. No. 150 732 in Mice After 3-Month Administration in the Diet, and Pathology Report.

Author: K. Schilling

Report Issued: April 25, 1986

Conclusions:

NOEL < 4000 ppm (M - 1000 mg/kg/day; F - 1467 mg/kg/day)

LEL = 4000 ppm (M - 1000 mg/kg/day; F - 1467 mg/kg/day) based on decreased body weight gain in males and females. In addition, at 8000 and 16,000, ppm there was an increase in water intake in males and females and BUN in males. There was decreased kidney weight in males and females and relative kidney weight in males in the 16,000 ppm group.

Classification: Core-Supplementary

The study does not satisfy the requirement for a Guidelines Series 82-1 90-day feeding study in rodents (A NOEL could not be established).

1/ Male (92 days); female (93 days).

* incl. summary of range finding study

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A. Materials:

1. Test Compound - Reg. No. 150 732; Description - not reported; Batch No. N 57 III/2; Purity - 98.29%.

2. Test Animals - Species: Mouse; Strain: B6C3F1/CrlBR; Age: 49 days; Weight: Males 22.5 (54.2-24.1) g, Females 19.1 (18.0-20.2) g; Source: Charles River Wiga GmbH, FRG.

B. Study Design:

1. Animal Assignment - Animals were assigned to the following test groups:

Test Group	Dose in Diet (ppm)	Main Study 3 Months Male	Female
1 Control	0	10	10
2 Low (LDT)	4000	10	10
3 Mid (MDT)	8000	10	10
4 High (HDT)	16000	10	10

The mice were singly housed in type M1 Macrolon cages with wire mesh tops. The mice were placed on racks in a room with temperature of 20 to 24 degrees C, relative humidity of 30 to 70 percent, and a 12-hour-on/12-hour-off light cycle.

2. Diet Preparation - Diet was prepared at intervals of not more than 4 weeks. The test material was characterized and the homogeneity was verified before the study began in a comparable batch (batch N 10) for a period of 2 years. Prior to study initiation, the homogeneity of the test substance mixture and the stability of the test substance in the feed was determined for a period of 30 days in study Nos. 30S0117/8321 and 30S0117/8337. Each dose level was prepared separately. A premix was made by mixing the test material in a small portion of the feed. This premix was then mixed with the appropriate amount of feed to achieve the appropriate test diets. Two samples of each test diet were analyzed at the beginning and end of the experiment.

Results - Generally, homogeneity produced values that were close to target values (in one study) of 100, 400, 1600, and 6400 ppm. The values varied less than 10 percent of target concentrations. A sample containing a mean of 42.2 ppm of the test material was sampled after 10 and 30 days and provided mean values of 41.7 and 41.3 ppm, respectively, indicating stability over a 30-day period. At the beginning of the study, mean values of

4092, 8252, and 17,602 ppm were obtained for target values of 4000, 8000, and 16,000 ppm of diet, respectively. At the end of the study, mean values at 4323, 9256, and 18,996 ppm were obtained for target values of 4000, 8000, and 16,000 ppm of diet, respectively.

3. Animals received food (Kliba maintenance diet rat/mouse/hamster, GLP 343 meal) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: ANOVA and Dunnett's test.

5. Quality assurance was conducted on January 6, January 22, March 14, and April 16, 1986. The statement was signed by R. Rosabacher on August 10, 1988.

C. Methods and Results:

1. Observations - Animals were inspected daily for signs of toxicity and twice daily for mortality.

Results - Toxicity - No signs indicative of toxicity were observed.

Mortality (Survival) - No deaths occurred.

2. Body Weight - Animals were weighed weekly for 3 months.

Results - Body weight gain was significantly decreased in males and females in the 4000, 8000, and 16,000 ppm groups (see Table 1 below - reviewer calculated):

Table 1. Mean Body Weight Gain (g)

Dose Level (ppm)	Interval (Days)			
Males	0 to 28	28 to 63	63 to 91	0 to 91
0	3.8	3.1	1.6	8.5
4000	3.8	2.2	1.0	7.0 (17.6)*
8000	2.9	2.3	1.1	6.3 (25.9)
16000	2.2	2.3	1.1	5.6 (34.1)

*Percent decrease in body weight gain relative to controls.

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Table 1. Mean Body Weight Gain (g) (cont'd)

Dose Level (ppm)	Interval (Days)			
Females	0 to 28	28 to 63	63 to 91	0 to 91
0	4.2	2.3	1.0	7.5
4000	4.0	1.3	0.8	6.1 (18.7)
8000	3.2	1.7	0.8	5.7 (24.0)
16000	2.7	1.8	1.0	5.5 (26.7)

3. Food Consumption, Water Intake, and Compound Intake - Consumption was determined and mean daily diet consumption was calculated weekly. Efficacy and compound intake were calculated once a week from the consumption and body weight gain data. Water intake was determined each week for the course of 2 days.

Results - Food consumption was comparable among control and treated animals. Food consumption was significantly increased in the treated animals at a few time intervals; however, the increase was attributed to food spillage. Examination of individual animal food consumption data supports the author's conclusion.

Food Efficiency - There were sporadically obtained "significantly" reduced values in treated groups that were attributed to food spillage. There were significant variations among groups and within groups indicating that the reduced feed efficiency, at certain intervals, may not be of biological importance.

Mean Compound Intake for males in the 4000, 8000, and 16,000 ppm groups was 1000, 2202, and 4555 mg/kg/day, respectively. For females in the 4000, 8000, and 16,000 ppm groups, mean compound intake was 1467, 2735, and 5953 mg/kg/day, respectively.

Mean Water Intake - Water intake was significantly increased in males and females in the 8000 and 16,000 group. On day 91, water intake was increased by at least 23.6 percent in these two dose groups.

Table 2. Mean Water Intake (g/kg bwt/day)

Dose Level (ppm)	Interval (Days)				
Males	7	28	63	91	
0	288.7	223.5	189.9	183.3	
4000	284.5	238.6	216.8	195.9	(6.9)*
8000	308.0	268.8	224.6	226.5	(23.6)
16000	317.0	304.9	260.2	253.6	(38.4)
Females					
0	288.6	248.9	230.5	199.2	
4000	298.0	246.8	237.7	226.2	(13.6)
8000	301.5	267.9	253.1	249.0	(25.1)
16000	347.4	319.4	273.5	274.6	(37.9)

*Percent increase in water intake relative to controls.

4. Ophthalmological Examinations were not performed.

5. Blood was collected at 92 or 93 days for hematology and clinical analysis from all animals. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*		Leukocyte differential count*
X	Hemoglobin (HCB)*		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*		Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*	X	Reticulocyte count
X	Blood Clotting Measurements (Thromboplastin time) (Clotting time) (Prothrombin time)		

*Required for subchronic and chronic studies.

Results - The MCV was marginally decreased in treated males showing a dose-response relationship. Males in the 0, 4000, 8000, and 16,000 ppm group had mean MCV values of 43.50, 42.70, 42.54, and 42.41 units FL (femtoliters). Statistical significance at $p < 0.01$

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was present in all male treated groups. However, because the decrease was very slight, no other hematological parameter characteristic of anemia was present and females failed to exhibit decreases in the MCV, little significance is attributed to the findings. The monocyte count and eosinophil count appeared to show a slight decrease in treated males. The decrease in monocyte count exhibited a dose-response relationship, whereas the decrease in the eosinophil count did not. Corresponding decreases in female mice were not apparent. Little significance is given to these findings.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
	Phosphorus*		Cholesterol*
	Potassium*		Globulins
	Sodium*		Glucose*
	Enzymes		Total bilirubin
	Alkaline phosphatase (ALK)		Total serum protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatinine phosphokinase*		Serum protein electrophoresis
	Lactic acid dehydrogenase (LAD)		
	Serum alanine aminotransferase (also SGOT)*		
	Serum aspartate aminotransferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

*Required for subchronic and chronic studies.

Results - Blood urea nitrogen (BUN) was significantly ($p < 0.05$) increased in males in the 8000 and 16,000 ppm groups. The BUN was 8.28, 8.98, 9.19, and 9.25 mmol/L in the 0, 4000, 8000, and 16,000 ppm groups. The increases in BUN may relate to the reduction in the absolute kidney weight of males in the treated groups (see Sacrifice and Pathology section).

6. Urinalysis was not conducted.

7. Sacrifice and Pathology - All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were

collected for histological examination. The (XX) organs, in addition, were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	X	Aorta*	X	Brain*
	Salivary glands*	X	Heart*	X	Periph. nerve*‡
X	Esophagus*	X	Bone marrow*	X	Spinal cord
X	Stomach*	X	Lymph nodes*		(3 levels)*‡
X	Duodenum*	X	Spleen	X	Pituitary
X	Jejunum*	X	Thymus*	X	Eyes (optic
X	Ileum*		Urogenital		nerve)*‡
X	Cecum*	XX	Kidneys		Glandular
X	Colon*	X	Urinary bladder*	XX	Adrenal gland*
X	Rectum*	XX	Testes*		Lacrimal gland‡
XX	Liver*	X	Epididymides	X	Mammary gland*‡
X	Gallbladder*	X	Prostate	X	Parathyroids*
X	Pancreas*	X	Seminal vesicle	X	Thyroids*
	Respiratory	X	Ovaries*		Other
X	Trachea*	X	Uterus*	X	Bone*‡
X	Lung*			X	Skeletal muscle‡*
	Nose^			X	Skin*‡
	Pharynx^			X	All gross lesions
	Larynx^				and masses*

*Required for subchronic and chronic studies.
^Required for chronic inhalation.
‡In subchronic studies, examined only if indicated by signs toxicity or target organ involvement.

Histological examination was conducted on tissues from all animals in the 0 to 16,000 ppm groups. In addition, the lungs, liver, and kidneys and gross lesions were examined in the 4000 and 8000 ppm groups.

Results

a. Organ Weight - There were statistically significant dose-related decreases in the absolute kidney weights of males in all treated groups and of females in the 16,000 ppm group. It was also reported that the absolute liver weights of females in all treated groups were significantly (statistically) decreased. The data are presented in Table 3 below. Included are the relative organ weights calculated by the reviewer using final body weights as determined on day 91 for comparable purposes.

Table 3. Organ Weights

(ppm)	Absolute (g)		Relative (%)[1]	
Males	Liver	Kidneys	Liver	Kidneys
0	1.084	.467	3.49	1.50
4000	1.093	.443*	3.69	1.50
8000	1.038	.420**	3.62	1.46
16000	1.075	.357**	3.84	1.28
Females				
0	1.090	.352	4.10	1.32
4000	1.014*	.350	4.02	1.39
8000	.991**	.339	3.98	1.36
16000	.999**	.310**	4.09	1.27

* $p < 0.05$
** $p < 0.01$
[1] Statistics not done

As previously indicated in the body weight section, body weights decreased as dosage increased, which could also affect absolute organ weight values. Although absolute kidney weights were reduced in all male treated groups, the decrease was only large in the 16,000 ppm group. On a relative weight basis, only the kidney weight in the male 16,000 ppm group is significantly lower. The absolute kidney weight was also decreased in the female 16,000 ppm group. Statistically significant decreases in the absolute weight of the liver occurred in all female treated groups, but the magnitude of the decrease was small and did not appear to be biologically significant. Also, a strict dose-response relationship was not evident. Based on a relative weight basis there was no difference in liver weights in females. This reviewer believes that only the decrease in the absolute and relative weight of the kidney in males and absolute kidney weight of females in the 16,000 ppm group is of significance.

b. Gross Pathology - Unremarkable.

c. Microscopic Pathology - Unremarkable.

D. Discussion:

No clinical signs of toxicity were observed and no deaths occurred. There was a dose-related decrease in male and female body weight gain. The decreases were at least

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17.6 to 18.7 percent of control body weight gain in the male and female 4000 ppm groups, respectively, and greater at higher dose levels. Food consumption was quite variable due to food spillage. Water intake was increased in the male and female 8000 and 16,000 ppm groups by at least 23.6 percent on day 91. The BUN was increased in males in the 8000 and 16,000 ppm groups. (The increase in BUN may correspond to decreased kidney weights.) In addition, there was a decrease in absolute (24%) and relative (15%) kidney weights of males and absolute weight (12%) of kidney in females in the 16,000 ppm groups. No corresponding microscopic pathology was present.

[It was noted that in the 4-week range-finding study (BASF No. 86/0056), focal interstitial inflammation, focal fatty infiltration, and bile duct proliferation in the liver was noted in three of five males in the 16,000 ppm group.]

The following range-finding study was examined and conclusions drawn. A DER will not be completed for this study.

Title: Report on the Study of the Subacute Toxicity of Reg. No. 150 732 in Mice After 4 Weeks Administration in the Diet (Range-Finding Study) (BASF #86/0056; 3/18/86) MRID No. 410635-17.

Summary - The test material was fed to B6C3F1/Crl Br mice at 0, 1000, 4000, 8000, and 16,000 ppm in the diet for 4 weeks. SGPT was increased in one of five males in the 16,000 ppm group. Three of five males in the 16,000 ppm had focal subacute interstitial inflammation, focal fatty infiltration, and bile duct proliferation in the liver.

NOEL = 8000 ppm (1200 mg/kg/day)

LEL = 16,000 ppm (2400 mg/kg/day)

Core-Supplementary

NOV 1 2 1990

Reviewed by: William B. Greear, M.P.H. William B Greear 6/20/90
Section II, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. Marion P. Copley
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 82-1
3-Month[1] Feeding - Mouse

TOX. CHEM NO: 325A

MRID NO.: 410635-19

TEST MATERIAL: Reg. No. 150 732

SYNONYMS: BAS 514..H, quinclorac

STUDY NUMBER: BASF 88/0338

SPONSOR: BASF

TESTING FACILITY: BASF Aktiengesellschaft
Department of Toxicology
6700 Ludwigshafen, FRG

TITLE OF REPORT: Report on the Study of the Oral Toxicity of Reg. No. 150732 in Mice After 3-Months Administration in the Diet, and Pathology Report

AUTHOR(S): K. Schilling

REPORT ISSUED: August 11, 1988

CONCLUSION: NOEL = 500 ppm (75 mg/kg/day) (HDT)

Classification: core-Supplementary (only 1 dose level was tested)

Acceptability: The study does not satisfy the requirement for Guideline Series 82-1 Subchronic Oral Toxicity.

Special Review Criteria (40 CFR 154.7)

[1] 98 days

A. MATERIALS:

1. Test compound: Reg. No. 150 732, Description not reported. Batch # N 57 III/2, Purity 98.29%

2. Test animals: Species: mouse, Strain: B6C3F1/CrlBR, Age: 49 days, Weight: male-23(22.6-24.2)g; female-19(18.6-20.5)g, Source: Charles River Wiga GmbH, FRG.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned to the following test groups:

Test Group	Dose in doet (ppm)	Main Study 3-month male	female
1 Cont.	0	10	10
2 High (HDT)	500	10	20

The mice were housed singly in type MII Makrolon cages with wire mesh tops. The mice were placed on racks in a room with temperature of 20-24°C, relative humidity of 30-70% and a 12 hour on/12 hour off light cycle.

2. Diet preparation

Diet was prepared at intervals of not more than 4 weeks. The test material was characterized and homogeneity was verified before the study began in a comparable batch (batch N10) for a period of 2 years. Prior to study initiation, the homogeneity of the test substance in the feed was determined for a period of 30 days in studies #30S0117/8337 and #30S0117/83 1. A premix was made by mixing the test material in a small portion of the feed. This premix was then adjusted to the desired concentration with the appropriate amount of feed. Two samples were taken at the beginning and the end of the experiment.

Results - Generally, the homogeneity produced values that were close to the target values (in 1 study) of 100, 400, 1600 and 6400 mg/kg. The values varied less than 10% of target concentrations. A sample containing a mean of 42.2 mg/kg of the test material, sampled after 10 and 30 days provided mean values of 41.7 and 41.3 mg/kg, respectively, indicating stability over a 30 day period. At the beginning and end of the study, mean values of 518 and 502 ppm, respectively, were obtained for the target concentration of 500 ppm.

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3. Animals received food (ground Kliba maintenance diet rat/mouse/hamster, GLP 343 meal) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: ANOVA and Dunnett's test.

5. Quality assurance was conducted on July 27, September 17 and November 30, 1987. The statement was signed by R. Rossbacher on August 10, 1988.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected daily for signs of toxicity and mortality. Once a week the animals were subjected to additional inspection and palpation.

   Results - Toxicity - No signs indicative of compound related toxicity were observed.
   Mortality (survival) - No deaths occurred.

2. Body weight - Animals were weighed weekly for 3 months.

   Results - Females in the 500 ppm group had slightly (although statistically significant) reduced body weights when compared to controls on day 98. This decrease was minimal and is not believed to be compound related since body weights were not significantly different at any other time intervals.

3. Food consumption, water intake and compound intake

   Consumption was determined and mean daily diet consumption was calculated weekly. Efficiency and compound intake were calculated once a week from the consumption and body weight gain data. Water intake was determined each week for the course of 1 day.

   Results - Food Consumption was comparable among animals in the control and treated groups. Some variation was present but can probably be attributed to food spillage.

   - Feed Efficiency varied from group to group and interval to interval. Differences could probably be attributed to food spillage.

   - Compound Intake varied for treated males and females from 71.8-96.4 mg/kg/day and from 121.5-138.3 mg/kg/day, respectively. Due to problems with food spillage, it was decided to use the standard conversion factor for the mouse (1ppm=0.15 mg/kg/day).

- Water Intake was comparable among the animals in the control and treated group.

4. Ophthalmological examinations were not performed.

5. Blood was collected before treatment and at 102 days for hematology and clinical analysis from 10 animals/sex group. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)
X	Platelet count*	X	Reticulocyte count

Results - There was a statistically significant decrease in the reticulocyte count for treated males (value 19) when compared to controls (value 22). However, the value was within normal limits. In addition, a decrease was not observed in treated females and, therefore, is probably not treatment related.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
	Phosphorous*		Cholesterol*
	Potassium*		Globulins
	Sodium*		Glucose*
	Enzymes		Total bilirubin
	Alkaline phosphatase (ALK)		Total serum Protein (TP)*
	Cholinesterase (ChE)#		Triglycerides
	Creatinine phosphokinase*^		Serum protein electrophoresis
	Lactic acid dehydrogenase (LAD)		
X	Serum alanine aminotransferase (also SGPT)*		
	Serum aspartate aminotransferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic and chronic studies

Results - Creatinine levels were increased in treated female mice at termination when compared to controls. However the value observed in treated female mice is comparable to the

values found in the control and treated males. When evaluated on its own merits, the increased creatinine value in treated females is probably of little biological significance.

6. Urinalysis was not conducted.

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination. No tissues were processed and no histopathological investigations were performed. The liver, kidneys, adrenals and testes were weighted.

Results

a. Organ weight - Unremarkable

b. Gross pathology - Unremarkable

c. Microscopic pathology was not conducted.

D. DISCUSSION:

There were no compound-related adverse effects observed in the 500 ppm treated group when compared to controls. Therefore, this study by itself is not adequate to predict a MTD for a mouse oncogenicity study.

* Recommended by Subdivision F (Oct. 1982) guidelines for chronic studies.

WGMOUSE/lca

EPA No.: 68D80056
DYNAMAC No.: 275-C
TASK No.: 2-75C
April 23, 1990

DATA EVALUATION RECORD

QUINCLORAC (REG NO. 150 732)

Chronic Toxicity/Oncogenicity Feeding Study in Rats

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Robert J. Weir

Date: 4/23/90

EPA No.: 68D80056
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April 23, 1990

DATA EVALUATION RECORD

QUINCLORAC (REG. NO. 150 732)

Chronic Toxicity/Oncogenicity Feeding Study in Rats

REVIEWED BY:

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Date: April 23, 1990

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DATA EVALUATION RECORD

GUIDELINE § 83-5

STUDY TYPE: Chronic toxicity/oncogenicity feeding study in rats.

MRID NUMBER: 410635-22.

TEST MATERIAL: 3,7-Dichloro-8-quinolinecarboxylic acid; Reg. No. 150 732.

SYNONYM: Quinclorac.

STUDY NUMBER: BASF: 88/0409.

SPONSOR: BASF Corporation, Chemicals Division, Parsippany, NJ.

TESTING FACILITY: BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, Federal Republic of Germany.

TITLE OF REPORT: Report on the Study of the Chronic Toxicity and Oncogenic Potential of Registration Number 150 732 in Rats: Administration via the Diet Over 24 Months.

AUTHOR: K. Schilling.

REPORT ISSUED: September 14, 1988.

CONCLUSIONS: Quinclorac (Reg. No. 150 732) was fed to groups of 50 rats/sex for 2 years at levels of 0, 1,000, 4,000, or 8,000 ppm and to groups of 20 rats/sex at levels of 0, 1,000, 4,000, 8,000, or 12,000 ppm; an additional 10/sex/group fed the higher levels were sacrificed at week 52. Body weights were slightly reduced in females receiving 12,000 ppm when compared to controls, but there were no effects on mean weights or weight gains in males. Water consumption was increased in both sexes, primarily at 4,000, 8,000, and 12,000 ppm, but this was not considered of toxicologic importance. No effects were seen on survival, food consumption, clinical signs of toxicity, clinical laboratory findings, organ weight, or gross or histologic findings. There was no oncogenic response. A maximum tolerated dose (MTD) was not established for the oncogenicity part of the study; the NOEL was equal to or greater than 8000 ppm. In the chronic toxicity part of the study, the LOEL in females was 12,000 ppm based on slight decreases in mean body weights, and the NOEL was 8,000 ppm; a LOEL was not established for males, and the NOEL was ≥12,000 ppm.

CORE Classification: The study is Core Supplementary for oncogenicity (Guideline 83-2) since the 8000 ppm dose was insufficient and at 12,000 ppm there were not sufficient animals (20/sex) to evaluate carcinogenicity; in addition, there is a probability of misdiagnosis of microscopic findings caused by tabulation of NAD (No Abnormalities Detected)* for tissues in several animals with severe postmortem autolysis. The study is also CORE Supplementary for chronic toxicity (Guideline 83-1) since an effect level was not established for males and because of the above problems with histopathology. The classifications are preliminary and may be upgraded after additional information (validation of histopathology) is provided by the sponsor.

A. MATERIALS:

1. Test Compound: Reg. No. 150 732 (quinclorac); description: not given (crystalline); batch Nos. and purity: III, N55--97.4%; III/2, N57--98.3%.

2. Test Animals: Species: rat; strain: Wistar (Chbb-THCM age: 42 days at initiation; weight: males--mean 184-18[illegible] g (range 164-201 g), females--mean 136-138 g (range 12[illegible]-160 g); source: Dr. Karl Thomae, GmbH, Biberach/Riss Federal Republic of Germany.

B. STUDY DESIGN:

1. Animal Assignment: Animals were acclimated to laboratory conditions for 9 days and were assigned randomly by sex to the following test groups:

* It may be possible to upgrade this study provided the sponsor provides an explanation for including the dose levels used concurrent with the data from the study for including NO dose levels.

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Test Group	Dose in Diet (ppm)	Main Study[a] (24 Months) Males	Females	Satellite Group I[b] (24 months) Males	Females	Satellite Group II[b] (12 months) Males	Females
1 Control	0	50	50	20	20	10	10
2 Low (LDT)	1,000	50	50	20	20	10	10
3 Mid (MDT 1)	4,000	50	50	20	20	10	10
4 Mid (MDT 2)	8,000	50	50	20	20	10	10
5 High (MDT)	12,000			20	20	10	10

[a]For evaluation of carcinogenicity.
[b]For evaluation of chronic toxicity.

Rats were housed singly in cages in air-conditioned rooms with a temperature range of 20-24°C, a humidity range of 30-70% and a 12-hour light/dark cycle.

The dose levels were selected on the basis of a 90-day study in rats fed quinclorac (Reg 150 732) at levels of 1,000, 4,000, or 12,000 ppm. Body weight and food consumption were reduced at the highest dose in both sexes and water consumption was increased. The serum activity of glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase was increased in males receiving 12,000 ppm; hematocrit, hemoglobin and mean corpuscular hemoglobin was reduced in females receiving 12,000 ppm. A minimal to slight focal chronic interstitial nephritis was seen in high-dose males. In previous range-finding studies, body weight and food consumption were reduced at 15,000 and 30,000 ppm in both sexes. In 30,000-ppm males, platelets and lymphocytes were decreased and several clinical chemistry parameters were affected. Nephropathy was observed in both sexes at 15,000 and 30,000 ppm, and cloudy swelling of hepatocytes was observed in 30,000-ppm males and females. Data were not available for review.

2. Diet Preparation: The test substance was weighed out and mixed thoroughly with a small amount of feed in a Bosch household mixer. Additional feed was added in appropriate amounts to obtain the desired concentration and stirred for 10 minutes in a laboratory mixer. Fresh diets were prepared at 1- to 3-week intervals. The homogeneity of each batch of test substance was analyzed, and the stability of the test substance preparations was confirmed over a 30-day period. The concentrations of mixture containing the test substance were evaluated at the start

of the study and thereafter at approximately 3-month intervals.

Results: Data for dietary analyses were found in MRID No. 410635-23 (Report 88/5114, pp. 1050-1061). Homogeneity analyses of diets at nominal levels of 1,000 and 12,000 ppm were performed at approximately 9 and 12 months. The coefficients of variance of homogeneity (8 samples) were between 0.6 and 2.6% for the four diets analyzed; 1,000-ppm diets were 99 or 107% of nominal, and 12,000-ppm diets were 96 or 105% of nominal. The mean (± S.D.) concentrations in diets at quarterly intervals between 3 and 18 months of the rat study were 101 ± 5.0, 102.7 ± 6.8, 102 ± 2.6, and 99.4 ± 5.3% of the target levels at 1,000, 4,000, 8,000, or 12,000 ppm. Stability data were not found.

3. Food and Water Consumption: Animals received food (Kliba rat/mouse/hamster maintenance diet ("A" GLP 343 meal; Klingentalmuhle AG, Switzerland) and water ad libitum.

4. Statistics: The following procedures were utilized in analyzing the numerical data: The means and standard deviations were calculated for data on food consumption, water consumption, body weight, feed efficiency, test substance intake, hematology, and clinical chemistry. The clinical data (body weights, hematology with the exception of differential blood count, and clinical chemistry) were analyzed by analysis of variance (ANOVA) followed by Dunnett's test. Urinalysis data were analyzed using the Chi-square test in appropriate 2 by 2 contingency tables.

   Organ weights were analyzed with Dunnett's test and gross findings were evaluated by the Fisher exact test using pairwise comparison with controls.

   Fisher's exact test was used for analysis of histologic findings; however, for the analysis, data were separated into (a) animals at terminal sacrifice and (b) those found dead or sacrificed in extremis. For (b), pairwise comparison was made between all groups and for (a) pairwise comparison was between controls and the highest-dose (8,000 ppm in the main study and 12,000 ppm in the satellite groups). For lungs livers and kidneys, analysis was performed for all animals (decedents and scheduled sacrifice) but main groups and satellite groups were not combined.

5. Quality Assurance: A quality assurance statement was signed and dated September 14, 1988. The Pathology Report quality assurance authorization was signed and dated September 7, 1988.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected daily for visible signs of toxicity. Each rat also received a detailed clinical examination including palpation for tissue masses weekly. Clinical observations were not recorded at weeks 4, 89, 93, or 101 and were only recorded every second week between 14 and 52 weeks.

   Results: Table 1 presents selected data on mortality and percent survival. No effects of dosing on survival were observed. In the main study, survival was 66 to 84% in all groups at termination. In the satellite groups, mortality did not differ in males and females receiving 12,000 ppm from that of other dosed groups or controls.

   No changes in behavior and clinical signs that were related to dosing were noted. The signs observed were generally those expected in aging rats. The incidence of animals with palpable masses was not increased by dosing. Polyurea (increased urination) was observed with an increased incidence and frequency in satellite males receiving 4000 ppm (3/20, 55 times) and 8000 ppm (3/20, 16 times) and in satellite females receiving 8000 ppm (2/20, 59 times) and 12,000 ppm (3/20, 173 times) when compared to controls (see Reviewers Discussion and Interpretation of Results).

2. Body Weight: Body weights were recorded weekly during the first 14 weeks and at 4-week intervals thereafter. Weight gain data were not provided.

   Results: Table 2 summarizes representative data on mean body weights. No significant differences were observed at dietary levels up to 8000 ppm. Mean body weights in males receiving 12,000 ppm were similar to controls through most of the study but were marginally lower (7%) at termination. In females receiving 12,000 ppm, mean body weights were significantly ($p < 0.05$ or 0.01) lower than controls from weeks 74 to 94 (maximum about 12%), and were 9% lower than in control females at termination. The weight gain in the second year of the study was approximately 37 g compared to 71 g for controls.

TABLE 1. Cumulative Mortality and Percent Survival in Rats Fed Quinclorac (Reg. No. 450 732) for 2 Years[a]

Dietary Level (ppm)	Cumulative Mortality and (Percent Survival) at Day: Satellite Group I			Main Study Group		
	364	546	728	364	546	728
			Males			
0	0 (100)	1 (95)	6 (70)	2 (96)	6 (88)	16 (68)
1,000	0 (100)	1 (95)	4 (80)	1 (98)	3 (94)	15 (70)
4,000	0 (100)	1 (95)	3 (85)	0 (100)	1 (98)	9 (82)
8,000	1 (95)	1 (95)	4 (80)	1 (98)	2 (96)	10 (80)
12,000	0 (100)	0 (100)	6 (70)	--	--	--
			Females			
0	0 (100)	1 (95)	4 (80)	0 (100)	0 (100)	14 (72)
1,000	0 (100)	2 (90)	4 (80)	0 (100)	4 (92)	15 (70)
4,000	0 (100)	1 (95)	5 (75)	2 (96)	3 (94)	17 (66)
8,000	0 (100)	2 (90)	9 (55)	0 (100)	0 (100)	8 (84)
12,000	0 (100)	1 (95)	6 (70)	--	--	--

[a]Percent survival was based on 50 rats/sex/dose of the main group and 20 rats/sex/dose in satellite group I. There was no mortality among the 10 rats/sex/dose in satellite group II (52-week sacrifice).

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TABLE 2. Mean Body Weights at Selected Intervals in Rats Fed Quinclorac (Reg. No. 150 732) for 2 Years

Dietary Level (ppm)	Mean Body Weight (g ± S.D.) at Week: 0	7	13	50	82	104
Males						
Main Groups						
0	186 ± 7	382 ± 28	447 ± 34	625 ± 62	705 ± 95	679 ± 107
1000	185 ± 7	385 ± 29	451 ± 39	638 ± 75	715 ± 82	695 ± 110
4000	183 ± 8	387 ± 27	452 ± 38	628 ± 65	702 ± 90	715 ± 79
8000	183 ± 7	377 ± 25	438 ± 31	614 ± 58	683 ± 86	702 ± 109
Satellites						
0	186 ± 8	386 ± 29	450 ± 41	615 ± 69	690 ± 95	715 ± 106
12,000	186 ± 7	380 ± 25	446 ± 30	618 ± 59	681 ± 74	673 ± 100
Females						
Main Groups						
0	139 ± 7	236 ± 21	267 ± 26	350 ± 44	384 ± 49	425 ± 69
1000	138 ± 7	233 ± 19	264 ± 22	345 ± 43	386 ± 61	413 ± 73
4000	138 ± 7	238 ± 17	268 ± 20	355 ± 42	391 ± 61	414 ± 80
8000	138 ± 7	231 ± 16	262 ± 19	337 ± 37	373 ± 51	395 ± 71
Satellites						
0	139 ± 7	234 ± 20	266 ± 22	345 ± 38	389 ± 48	402 ± 68
12,000	138 ± 7	234 ± 15	267 ± 18	329 ± 33	342 ± 38**	366 ± 50

**Significantly different from control value, $p \leq 0.01$.

3. Food Consumption, Water Consumption, and Compound Intake: Food consumption was determined weekly during the first 1[illegible] weeks and at 4-week intervals thereafter for both main and satellite groups. Water consumption was determined at the same intervals in the satellite groups.

Results: Food consumption and food efficiency were not affected by dosing. Water consumption data are summarized in Table 3. Water consumption (satellite group I rats) was increased in males and females receiving 8,000 and 12,000 ppm when compared to controls. It also tended to be increased in males and females receiving 4000 ppm, but there was not a clear dose-related trend.

The time-weighted average compound intake was 56, 186, 385, and 587 mg/kg/day for males and 60, 235, 478, and 757 mg/kg/day for females at nominal dietary levels of 1,000, 4,000, 8,000, or 12,000 ppm, respectively.

4. Ophthalmology: Ophthalmic examinations were performed on control and high-dose rats in satellite group 1 before the start of the study and at 12 and 24 months.

Results: No effects related to dosing were observed.

5. Hematology and Clinical Chemistry: Blood was collected from the retro-orbital venous plexus. Samples were taken from the first 10 surviving animals (nonfasted)/sex/dose in satellite group I prior to study initiation and at 95, 193, 361, 557, and 725 days. Blood smears were also performed on fasted animals sacrificed at one year (Satellite II) and on all prematurely sacrificed rats. The CHECKED (X) parameters were examined:

a. Hematology:

X	Hematocrit (HCT)[1]	X	Leukocyte differential count
X	Hemoglobin (HGB)[1]	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)[1]	X	Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)[1]	X	Mean corpuscular volume (MCV)
X	Platelet count[1]	X	Prothrombin time (Hepato Quick's test)
X	Reticulocyte count (RETIC)		
X	Red cell morphology		

[1]Recommended by Subdivision F (November 1984) Guidelines.

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TABLE 3. Mean Water Consumption (g/day) in Rats Fed Quinclorac (Reg. No. 150 732) for 2 Years[a]

Dietary Level (ppm)	g Water/Day Between Months: 0-3	6-12	12-18	18-24
		Males		
0	26.3	30.1	30.2	35.3
1000	27.8	30.9	34.7	37.6
4000	26.7	30.4	34.4	51.1
8000	31.0	37.1	38.9	42.0
12,000	30.5	36.0	38.5	43.9
		Females		
0	20.3	26.1	32.2	38.2
1000	20.7	29.0	34.3	37.8
4000	21.5	28.9	37.4	43.6
8000	24.4	35.8	44.1	52.5
12,000	26.0	40.2	54.6	63.[illegible]

[a]Mean values were calculated by reviewers from weekly or monthly means in Tables 27 to 42 of Study Report.

Results: No effects of dosing on hematology parameters were observed. All mean values were within the normal range, there were no apparent trends, and changes in dosed groups that differed significantly from controls were considered incidental and were infrequent.

b. Clinical Chemistry:

	Electrolytes		Other
X	Calcium[1]	X	Albumin[1]
X	Chloride[1]		Albumin/globulin ratio
	Magnesium[1]	X	Blood creatinine[1]
X	Phosphorus[1]	X	Blood urea nitrogen[1]
X	Potassium[1]	X	Cholesterol[1]
X	Sodium[1]	X	Globulins
		X	Glucose[1]
	Enzymes	X	Total bilirubin[1]
X	Alkaline phosphatase (ALP)		Direct bilirubin
	Cholinesterase	X	Total protein[1]
	Creatine phosphokinase[1]	X	Triglycerides
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (SGPT)[1]		
X	Serum aspartate aminotransferase (SGOT)[1]		
	Gamma glutamyltransferase (GGT)		

Results: Clinical chemistry parameters were not affected by dosing. Mean values that were aberrant were infrequent and usually caused by an outlier value. Other values in dosed groups that significantly differed from controls were not considered of toxicologic importance since they were either not dose related or they were not consistent between intervals of analysis (e.g., urea--4000-ppm males, 27 weeks; triglycerides--1000 ppm males, 13 weeks and 4000-ppm males, 52 weeks; creatinine--8000-ppm females, 27 weeks; glucose--8000-ppm females, 79 weeks).

6. Urinalysis: Urine was collected overnight from each of the first 10 surviving animals from satellite groups at 91, 187, 355, 551, and 719 days after the study start. The CHECKED (X) parameters were examined:

X	Appearance[1]	X	Glucose[1]
	Volume[1]	X	Ketones
	Specific gravity[1]	X	Bilirubin[1]
X	pH	X	Blood[1]
X	Sediment (microscopic)[1]	X	Nitrite
X	Protein[1]	X	Urobilinogen

[1]Recommended by Subdivision F (November 1984) Guidelines.

Results: No effects of toxicologic importance were observed for any urinary parameters. A reduced protein concentration was observed in urine of males and females receiving 8,000 and 12,000 ppm for the urine collections at 18 and 24 months. This was reported to be caused by increased water consumption and urine volume. However, the volume and specific gravity of samples were not measured.

7. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subject to gross pathological examination, and the CHECKED (X) tissues were collected for histological examination. In addition, the (XX) organs were weighed for all animals subject to scheduled sacrifice:

	Digestive System		Cardiovasc./Hemat.		Neurologic
	Tongue	X	Aorta[1]	XX	Brain
X	Salivary glands[1]	X	Heart[1]	X	Peripheral nerve (sciatic nerve)[1]
X	Esophagus[1]	X	Bone marrow (sternal)[1]	X	Spinal cord (3 levels)
X	Stomach[1]	X	Lymph nodes[1]	X	Pituitary[1]
X	Duodenum[1]	X	Spleen	X	Eyes (optic nerve)[1]
X	Jejunum[1]	X	Thymus		
X	Ileum[1]				Glandular
X	Cecum[1]		Urogenital	XX	Adrenals[1]
X	Colon[1]	XX	Kidneys[1]		Lacrimal gland
X	Rectum	X	Urinary bladder[1]	X	Mammary gland[1]
XX	Liver[1]	XX	Testes[1]	X	Thyroids[1]
	Gallbladder[1]		Epididymides	X	Parathyroids[1]
X	Pancreas[1]	X	Prostate		Harderian glands
		X	Seminal vesicle		
	Respiratory	XX	Ovaries		Other
X	Trachea[1]	X	Uterus	X	Bone (sternum and femur)[1]
X	Lung[1]			X	Skeletal muscle[1]
				X	Skin
				X	All gross lesions and masses

In the main study, a complete complement of tissues was examined histologically for the control and 8000-ppm groups at the final sacrifice and in all groups for animals that

[1]Recommended by Subdivision F (November 1984) Guidelines.

died or were sacrificed moribund. In addition, lungs, liver and kidneys, and gross lesions were examined for all animals. In the satellite groups, similar examinations were performed for the control and 12,000-ppm groups. All protocol-specified tissues as well as all gross lesions were reported to be present, and no tissues from animals found dead or sacrificed in extremis were missing. (See Reviewers Discussion and Interpretation of Results).

Results:

a. Organ Weights: No effects on organ weights were observed in the main groups or satellite groups.

b. Gross Pathology: Table 4 presents a summary of frequent gross findings combining data for the main group and the satellite group that was scheduled for the 2-year sacrifice. No dose-related trends were apparent. Statistical analysis of data from the main group by the authors indicated a significant deviation from control incidence for the following: focus in the liver (males--8000 ppm), enlarged adrenal glands (females--8000 ppm), focus in the testes (males--4000 ppm), focus in the adrenal glands (females--4000 ppm), and cysts of the liver (females--1000 ppm). No significant increases in findings were seen in the satellite groups at 12,000 ppm when compared to their respective controls.

c. Microscopic Pathology:

1) Nonneoplastic: There were no notable findings at the 12-month sacrifice (Satellite II). Table 5 presents frequent findings in the liver, lung, and kidneys, and Table 6 presents data in the control and high-dose groups for other tissues for rats in the main groups and satellite II groups combined. Although the incidence of some findings increased or decreased sporadically in dosed groups of both sexes when data were separated by animal disposition or by main or satellite groups, there were no dose trends or changes indicating a toxic effect related to test compound.

2) Neoplastic: Table 7 summarizes the incidence of neoplastic findings. No significant increases or decreases in the incidence of neoplasms were observed when dosed groups were compared to controls. The types and incidence of neoplasms were similar in the main and satellite groups, and all were within the range normally seen for this strain of rat.

TABLE 4. Frequent Gross Findings in Rats Fed Quinclorac (Reg. No. 150 732) for 2 Years

Organ/Finding	Dietary Level (ppm): Males 0	1000	4000	8000	12000	Females 0	1000	4000	8000	12000
Liver	(70)[a]	(70)	(70)	(70)	(20)	(70)	(70)	(70)	(70)	(20)
Focus	35	34	36	41	9	28	28	16	21	6
Mass	4	6	4	5	1	2	5	1	0	0
Cyst	7	8	11	9	3	4	13	12	8	2
Lung	(70)	(70)	(70)	(70)	(20)	(70)	(70)	(70)	(70)	(20)
Focus	9	11	13	7	3	2	4	6	4	1
Pituitary	(70)	(70)	(70)	(70)	(20)	(70)	(70)	(70)	(70)	(20)
Mass	14	18	13	9	2	56	61	60	60	15
Adrenal	(70)	(70)	(70)	(70)	(20)	(70)	(70)	(70)	(70)	(20)
Enlarged	6	1	2	2	1	4	13	10	21	3
Mass	1	5	4	4	1	3	7	1	2	0
Focus	0	2	4	3	1	17	19	28	12	6
Testis	(70)	(70)	(70)	(70)	(20)					
Mass	4	11	9	8	2					
Focus	5	5	20	14	5					
Ovary						(70)	(70)	(70)	(70)	(20)
Mass						2	3	8	9	5
Cyst						12	11	12	15	2
Mammary gland						(70)	(70)	(70)	(70)	(20)
Mass						21	21	28	22	5
Pancreas	(70)	(70)	(70)	(70)	(20)	(70)	(70)	(70)	(70)	(20)
Mass	4	0	12	11	3	2	0	1	1	3

[a]The numbers in parentheses represent the number of animals examined (including main groups and satellite group I).

TABLE 5. Frequent Nonneoplastic Findings in Liver, Kidneys, and Lung of Rats Fed Quinclorac (Reg. No. 150 732) for 2 Years[a]

Organ/Finding	Dietary Level (ppm): Males 0	1000	4000	8000	12000	Females 0	1000	4000	8000	12000
Liver	(70)[b]	(70)	(70)	(70)	(20)	(70)	(70)	(70)	(70)	(20)
Focal fatty change	20	6	1	13	3	6	1	5	5	1
Cholangiectasis	1	0	1	0	0	3	11	11	7	3
Kidneys	(70)	(70)	(70)	(70)	(20)	(70)	(70)	(70)	(70)	(20)
Early changes of chronic nephropathy	29	30	36	30	11	33	45	46	36	12
Chronic nephropathy	31	26	30	30	4	12	13	12	15	6
Pelvic mineralization	25	30	30	41	8	46	60	60	57	16
Lung	(70)	(70)	(70)	(70)	(20)	(70)	(70)	(70)	(70)	(20)
Foam cell aggregation	11	10	15	14	8	13	12	13	8	1

[a]Includes all animals in the main groups and the satellite groups that were scheduled for 2 years on study; includes rats sacrificed at termination as well as rats that died or were sacrificed moribund.

[b]The numbers in parentheses represent the number examined.

TABLE 6. Frequent Nonneoplastic Lesions in Rats Fed Quinclorac (Reg. No. 150 732) for 2 Years[a]

Organ/Finding	Dietary Level (ppm): Males Main 0	Males Main 8000	Males Satellite I 0	Males Satellite I 12000	Females Main 0	Females Main 8000	Females Satellite I 0	Females Satellite I 12000
Heart	(50)[b]	(50)	(20)	(20)	(50)	(50)	(20)	(20)
Myocardial atrophy/ fibrosis	47	49	19	19	37	39	16	17
Spleen	(50)	(50)	(20)	(20)	(50)	(50)	(20)	(20)
Increased brown pigment	14	10	5	2	12	15	5	5
Pancreas								
Acinar cell hyperplasia	3	5	1	3	1	3	0	0
Pituitary gland	(50)	(50)	(20)	(20)	(50)	(50)	(20)	(20)
Hyperplasia	4	5	1	2	2	4	1	0
Adrenal gland	(50)	(50)	(20)	(20)	(50)	(50)	(20)	(20)
Cortical hyperplasia	10	7	5	3	5	2	0	2
Medullary hyperplasia	5	3	1	4	4	7	2	3
Thyroid	(50)	(50)	(20)	(20)	(50)	(50	(20)	(20)
C-cell hyperplasia	3	3	2	0	6	12	3	2
Testis	(50)	(50)	(20)	(20)				
Interstitial cell hyperplasia	6	9	0	5				
Eye	(50)	(50)	(20)	(20)	(50)	(50)	(20)	(20)
Cataract	7	11	2	8	1	3	1	1

[a]Only the incidence data in control and high-dose groups are tabulated. In other groups, histopathology was not complete (only for animals that died or for those with grossly observed lesions).

[b]The numbers in parentheses represent the number of tissues examined.

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TABLE 7. Neoplastic Lesions in Rats Fed Quinclorac (Reg. No. 150 732) for 2 Years[a]

Organ/Finding	Dietary Level (ppm): Males 0	1000	4000	8000	12000	Females 0	1000	4000	8000	12000
Multiple organs	(70)[b]	(70)	(70)	(70)	(20)	(70)	(70)	(70)	(70)	(70)
Malignant lymphoma	3	6	4	5	3	8	10	5	5	1
Liver	(70)	(70)	(70)	(70)	(20)	(70)	(70)	(70)	(70)	(70)
Neoplastic nodule	18	12	10	19	1	3	6	1	3	0
Hepatocellular carcinoma	3	4	3	2	1	0	0	0	0	0
Pituitary	(70)	(33)	(24)	(57)	(20)	(70)	(68)	(66)	(68)	(20)
Adenoma	23	18	13	17	3	59	58	61	56	18
Adrenal	(70)	(26)	(21)	(57)	(20)	(70)	(46)	(48)	(63)	(20)
Pheochromocytoma	15	8	6	10	4	2	3	5	3	2
Thyroid	(70)	(22)	(19)	(56)	(20)	(70)	(26)	(22)	(61)	(20)
C-cell adenoma	5	1	2	3	0	1	[illegible]	1	1	2
Pancreas	(70)	(28)	(28)	(58)	(20)	(70)	(23)	(24)	(58)	(20)
Acinar-cell adenoma	0	2	0	3	3	0	0	0	0	0
Acinar-cell adenocarcinoma	1	0	0	1	0	0	0	0	0	0
Testis	(70)	(43)	(37)	(62)	(20)					
Interstitial tumor	18	19	22	26	6					
Mammary gland						(70)	(42)	(44)	(64)	(20)
Adenoma						5	6	12	9	2
Fibroadenoma						6	9	7	5	2
Adenocarcinoma						1	2	0	2	1
Skin	(70)	(42)	(41)	(63)	(20)	(70)	(26)	(32)	(61)	(20)
Fibroma	2	3	0	6	1	0	1	0	0	1

[a]Neoplasms that were seen at an incidence of 3% or less or are considered incidental are not included. Data at the 52-week sacrifice (satellite II) are not included.

[b]The numbers in parentheses indicate the number of tissues examined.

D. STUDY AUTHOR'S CONCLUSIONS:

The administration of Quinclorac (Reg. No. 150 732) via the diet to rats for 2 years caused a slight body weight reduction in females receiving 12,000 ppm, but no effect in males at the same dose or in either sex at doses of 1000, 4000, or 8000 ppm. There was no effect of dosing on clinical signs or survival. Food consumption was not affected, but water consumption and urine output were increased in both sexes at levels of 4000 ppm and above; the effects on water consumption were not considered of pathognomonic (sic) importance. Hematology and clinical chemistry findings were not affected, and no changes in organ weights were found. There were no adverse effects on gross or histologic findings after dosing for 2 years at levels of up to 12,000 ppm. The test compound was not carcinogenic. The NOEL was above 12,000 ppm for males and between 8,000 and 12,000 ppm for females.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

Under the conditions of the study, there was no clear evidence of oncogenicity. However, it can be questioned if the study adequately tested the compound. At the highest dose tested (12,000 ppm), only 20 rats/sex were present for evaluation and an effect level was established for only one sex (females). At the 8000-ppm dose, 50 rats/sex were present, but a maximum tolerated dose (MTD) was not approached. The dose selection was based on a 90-day feeding study in rats dosed at 0, 1000, 4000, and 12,000 ppm. Body weights and food consumption were reduced in both sexes at 12,000 ppm in the 90-day study, and mean corpuscular hemoglobin was reported to be reduced in the high-dose females. Data were not available for our review. It was reported that in range-finding studies, body weights, food consumption, and several clinical chemistry parameters were affected at 15,000 and 30,000 ppm; nephropathy was seen in both sexes at these dose levels, and cloudy swelling of hepatocytes was seen in both sexes receiving 30,000 ppm.

It is our assessment that the dose levels were inadequate in the present oncogenicity study, and that the rats could have tolerated a higher dose. In the main study, the weight gain during weeks 1-50 (not calculated from individual animal data; calculated from means) in high-dose females was 6% lower than in controls; between 50 and 82 weeks it was comparable to controls (36 versus 34 g). In the satellite group of females receiving 12,000 ppm, the weight gain was 7% lower than that of controls between weeks 0 and 50 and 29% lower between weeks 50 and 82 (13 g versus 44 g). Weight changes later in the study are usually not considered reliable indicators of an effect. On the basis of weight-gain data, we conclude that an

MTD was approached in females at 12,000 ppm but not at 8,000 ppm, and an MTD was not established in males.

The reviewers also question the completeness of the histopathological examination. The histopathology report stated (P1304) that no protocol specified organs were missing in control and high-dose groups and that lungs, liver, and kidneys at all treatment levels and all tissues with gross lesions present. It also stated the no organs were missing for animals killed in extremis or found dead. Examination of the individual animal histopathology sheets indicated that NAD (no abnormality detected) was apparently entered for every tissue without a recorded histologic finding. It seems improbable, however, that no tissues were lost and it is probable that some were inadequate for evaluation because of autolysis. The reviewers checked the individual gross pathology records to assess the impact of autolysis. The data presented in Table 8 summarize the postmortem condition of rats that died. Since severe autolysis was present for nine rats in the main study and four in the satellite study and moderate autolysis was present in 15 rats, there is a probability for misdiagnosis and the sponsor should validate the histopathology results.

A nonsignificant increase in the incidence of acinar cell adenoma of the pancreas was observed in males receiving 8000 ppm in the main study and 12,000 ppm in the satellite study. The increase was significant ($p < 0.01$) at 12,000 ppm when results were combined for main and satellite groups (Table 9). Grossly observed masses in the pancreas were increased in males receiving 4000 and 8000 ppm ($p < 0.05$), and the incidence of acinar cell hyperplasia was also increased in dose males (Table 9). We assess that the pancreas should have been examined in all animals in the low and mid-dose groups (main and satellite 1) and the laboratory historical control incidence of acinar cell neoplasms be provided to adequately assess the findings in the pancreas.

Several outlier values were included in calculating means and standard deviations for clinical laboratory parameters (e.g., AST, urea, triglycerides, creatinine); data calculated by the reviewers omitting these aberrant values were more presentable, but the conclusions were not affected. Although the authors stated in their conclusions (p. 17 Section D) that urine output was increased at 4000 ppm and above, urine volume was not measured and clinical observation of polyurea indicated occurrence in three or less rats of either sex/dose group.

Mean values for adrenal gland weights that were two to three times greater than control (not significant) were noted for main group males receiving 4000 and 8000 ppm. These increases correlated with 15-mm masses weighing 4.79 g (animal No. 190) and 7.4 g (animal No. 280). The mass in animal No. 190 was a

TABLE 8. Postmortem State of Rats That Died or Were Sacrificed Moribund

Postmortem Condition	Dietary Level (ppm)									
	Males					Females				
	0	1000	4000	8000	12,000	0	1000	4000	8000	12,000
	Main Study (50 rats/sex/group)									
	(16)[a]	(15)	(9)	(10)	--	(14)	(15)	(7)	(8)	--
Bad	2	1	0	1	--	0	3	2	0	--
Moderate	1	5	1	0	--	2	0	0	2	--
	Satellite Group 1 (20 rats/sex/group)									
	(6)[a]	(4)	(3)	(4)	(6)	(4)	(4)	(5)	(9)	(6)
Bad	0	0	0	0	0	1	2	1	1	3
Moderate	0	0	0	1	0	1	1	0	1	0

[a]The numbers in parentheses are the number found dead or sacrificed in extremis.

TABLE 9. Pathologic Findings in the Pancreas of Males Fed Quinclorac

	Dietary Level (ppm)				
	0	1000	4000	8000	12,000
Masses					
Main Groups (50/group)	3	6	9	7	..
Satellites (20/group)	1	3	3	4	3
Total	4	9	12*	11*	3
Histology					
Main Groups	(50)[a]	(21)	(22)	(50)	..
Acinar cell adenoma	0	1	0	3	..
Acinar cell adenocarcinoma	0	0	0	1	..
Acinar cell hyperplasia	3	3	7*	5	.
Satellite Groups	(20)	(7)	(6)	8)	20)
Acinar cell adenoma	0	1	0	0	0
Acinar cell adenocarcinoma	1	0	0	0	0
Acinar cell hyperplasia	1	2*	1	0	0
All Animals					
Acinar cell adenoma	0/70	1/28	0/28	3/58	0/20**

[a]The numbers in parentheses are the numbers examined microscopically

*Significantly different from control incidence ($p < 0.05$), Fisher's Exact Test by the reviewers.

**Significantly different from control incidences ($p < 0.01$)

pheochromocytoma; no histological correlate was seen for animal No. 280. A satellite female (No. 484, 1000 ppm) had a 30-mm mass weighing 37.4 g on an adrenal that was diagnosed as a pheochromocytoma. The mean value for the group calculated without this organ weight value was 0.19 g compared to the 2.55 g reported.

We agree with the study author's assessment that there were no effects on survival, clinical signs of toxicity, food consumption, clinical laboratory findings, and organ weight data. The increase in water consumption in dosed rats was not assessed of toxicologic importance. No changes in gross or histologic findings were clearly related to dosing with the possible exception of the changes in the adrenals of males discussed above. The NOEL in the oncogenicity portion of the study was greater than 8000 ppm. In the chronic portion of the study, the LOEL in females was 12,000 ppm based on slight body weight decrements, and the NOEL was 8,000 ppm. Effect levels were not established for males and would be higher than 12,000 ppm.

EPA No.: 68D80056
DYNAMAC No.: 275-B
TASK No.: 2-75B
May 23, 1990

DATA EVALUATION RECORD

QUINCLORAC (Reg. No. 150 732)

Chronic Dietary Toxicity Study in Dogs

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: William J. McFeeley for

Date: May 22, 1990

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EPA No.: 68D80056
DYNAMAC No.: 275-B
TASK No.: 2-75B
May 23, 1990

DATA EVALUATION RECORD

QUINCLORAC (Reg. No. 150 732)

Chronic Dietary Toxicity Study in Dogs

REVIEWED BY:

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Principal Reviewer
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DATA EVALUATION RECORD

GUIDELINE §83-1

STUDY TYPE: One-year dietary toxicity study in dogs.

MRID NUMBER: 411232-01.

TEST MATERIAL: Reg. No. 150 732.

SYNONYM: 3,7-Dichloro-8-quinolinecarboxylic acid; Quinclorac.

STUDY NUMBER: 88/0029.

SPONSOR: BASF Corporation Chemicals Division, Agricultural Chemicals, Parsippany, N.J.

TESTING FACILITY: BASF Aktiengesellschaft, Department of Toxicology, 6700 Ludwigshafen, Federal Republic of Germany.

TITLE OF REPORT: Report on the Study of the Toxicity of Registration Number 150 732 in Beagle Dogs After 12-Month Administration in the Diet.

AUTHOR: Hellwig, H.

REPORT ISSUED: January 6, 1988.

CONCLUSIONS: Quinclorac (Reg. No. 150 732) was administered to groups of 6 male and 6 female beagle dogs at dietary levels of 0, 1,000, 4,000, or 12,000 ppm for 12 months. No effect on mortality was observed. Administration of 12,000 ppm resulted in lower mean body weight, compared with control, reduced body weight gain and an adverse effect on food efficiency. There was a marginal reduction of body weight gain and food efficiency in male dogs fed 4,000 ppm of test substance. In male dogs fed 12,000 ppm of test substance, there were significant ($p < 0.01$) treatment-related reductions in hemoglobin concentration, erythrocyte count, and hematocrit, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) values. In females fed 12,000 ppm of test substance, significant reductions ($p < 0.05$ or $p < 0.01$) were seen in hemoglobin concentration, MCH, and MCV at all study intervals (weeks 13, 26, and 52), hematocrit at weeks 26 and 52 and erythrocyte count at week 26. In females fed 4000 ppm test substance, significant reductions ($p < 0.05$) were seen at week 26 in hemoglobin concentration, erythrocyte count, and hematocrit. Administration of 12,000 ppm of test substance resulted in decreases in a number of clinical chemistry parameters; however, significant ($p < 0.01$) changes were noted only for creatinine, calcium, and albumin. However, it should be noted that, in most cases, clinical adverse effects are only associated with increased values for these parameters. At the 12,000-ppm dose level, increases in absolute ($p < 0.01$ for males) and relative liver weights ($p < 0.01$ for both males and females) were observed for both sexes. Relative liver weights also were significantly increased ($p < 0.05$) in females of the 4,000- and 1,000-ppm groups. Relative kidney weights were significantly increased ($p < 0.01$) in both males and females of the 12,000-ppm group and in males of the 4,000-ppm group. There were no histopathologic correlates to account for the increased organ weights. Histopathologic findings in the liver were limited to an increase in focal mononuclear infiltration and to single cell necrosis in two dogs in the 12,000-ppm group. Hydropic degeneration of the kidney was seen in two males and two females of the 12,000-ppm group.

Based on the reduced body weight gain, adverse effect on food efficiency, hematological and clinical chemistry values, increased liver and kidney weights, and microscopic findings, the no-observed-effect level (NOEL) is 4,000 ppm (140 mg/kg/day: both sexes) and the lowest-observed-effect-level (LOEL) is 12,000 ppm (513 mg/kg/day--males, 469 mg/kg/day--females).

Classification: CORE Guideline.

A. MATERIALS:

1. Test Compound: Reg. No. 150 732; description: colorless, crystalline; batch Nos.: N32, used from study initiation until July 1985, and N55, used from July 1985 until end of study; purity: 96.5% (batch No. N32), 97.4% (batch No. N55).

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2. Test Animals: Species: dog; strain: beagle; age: about 6-9 months at initiation of the study; weight: at the initiation of treatment, males--6.9-10.3 kg (mean = 8.7 kg), females--7.1-10.7 kg (mean = 8.9 kg); source: BASF.

B. STUDY DESIGN:

1. Animal Assignment: Dogs were taken from the in-house breeding unit and acclimated to laboratory conditions for 3 to 4 weeks before initiation of treatment. They were free from signs of disease and had been previously vaccinated. The animals were randomly assigned by means of a random-number generator to the test groups having approximately equal mean body weight in the individual groups as follows:

Test Group	Dose in Diet (ppm)	Number of Animals	
		Males	Females
1 Control	0	6	6
2 Low (LDT)	1,000	6	6
3 Mid (MDT)	4,000	6	6
4 High (HDT)	12,000	6	6

Dose levels were selected on the basis of a previous 4-week range-finding study. In the range-finding study, two dogs/sex/group each received the test material daily in the diet for 4 weeks at dose concentrations of 0, 1,000, 3,000, 9,000, and 27,000 ppm. At 27,000 ppm, the main findings included reduced feed intake, marked loss of body weight, occasional vomiting, reduced alkaline phosphatase activity in the plasma, reduced absolute testes weight, and chronic interstitial glomerulonephritis. At 9,000 ppm, only alkaline phosphatase activity in the plasma was reduced. No compound-induced changes occurred at 3,000 ppm and 1,000 ppm. Based on these findings, 12,000 ppm was selected as the high dose; 4,000 ppm, and 1,000 ppm were the other doses selected for the 12-month study.

Animals were housed singly in individual kennels (5.4 m² floor space) with access to an outer kennel in animal rooms with an automatic ventilation system and having an illumination period that corresponded to the natural

day/night cycle, with artificial lights that additionally could be switched on as needed during working hours.

2. Diet Preparation: Test substance formulations were freshly prepared, usually at intervals of about 3 weeks. Premixes were prepared by adding the weighed test substance to a small portion of the feed and thoroughly mixing by using a spatula in a beaker. A premix was then adjusted to the required concentration by mixing with an appropriate amount of feed in a laboratory mixer (GEBR.LÖDIGE) for about 10 minutes. Before initiation of the study, after 3 and 6 months, and at the end of the study, dietary samples were analyzed for content of active ingredient, contaminants, and homogeneity. Two samples of each dose were sent for analysis at the beginning of the study and then at intervals of approximately 3 months for analysis of test substance formulations.

   Results: The test substance was found to be stable at room temperature over a period of 30 days. Analysis of batches N32 (before initiation of the study) and N55 (before its use as of July 1985) revealed an active ingredient content of 96.5% and 97.4%, respectively. Analysis of the pure test substance at the end of study showed a mean active ingredient content of 100%. Table 1 summarizes mean concentrations of test material in diets at various time intervals during the study. Mean concentrations (average of two analytical values) for the dietary target values were as follows: 86.6% to 107.7% for the 1,000-ppm dose level, 87.15% to 110.1% for the 4,000-ppm dose level, and 94.38% to 113.1% for the 12,000-ppm dose level. It was stated that the test substance was homogeneously distributed.

3. Food and Water Consumption: A ration of 700 g diet was given, consisting of 350 g powdered feed prepared from pellets (KLIBA laboratory diet "A") that had been made into a paste with 350 mL water in a food bowl immediately before administration to each dog daily. Water was provided ad libitum.

4. Statistics: Mean values and standard deviations were calculated for food consumption, body weight, body weight change, food efficiency, and test substance intake; mean values and standard deviation (of the individual values) were calculated for fasted body weight and absolute and relative organ weights of the animals in each test group. Statistical analysis was carried out using an analysis of variance (ANOVA) followed by Dunnett's test or a test by Williams for the simultaneous comparison of several dose groups with a control group.

TABLE 7. Mean Concentrations of Quinclorac (Reg. No. 150 732) Fed to Dogs[a]

Test Group	Target Value (ppm)	Mean Concentration (ppm) and % of Nominal at Study Weeks: 0	3	6	9	12
1	1,000	1,053 (105.3)[b]	1,077 (107.7)	1,014 (101.4)	1,019 (101.9)	866 (86.6)
2	4,000	4,180 (104.5)	4,404 (110.1)	4,107 (102.7)	4,277 (106.9)	3,486 (87.15)
3	12,000	12,312 (102.6)	13,576 (113.1)	11,325 (94.38)	13,018 (108.5)	11,950 (99.58)

[a]Data were extracted from study No. 88/0029, page 59.

[b]Numbers in parentheses are percentages.

5. Quality Assurance: A quality assurance statement was attached with name (Dr. H. Fleig) and date (December 4, 1987); however, a signature was not present. A GLP Statement of Compliance was signed by Jack R. Graham and dated February 21, 1989, stating that the study was conducted in accordance with "OECD Principles and Good Laboratory Practice" (Paris, 1981).

C. METHODS AND RESULTS:

1. Observations: Animals were inspected for overt signs of toxicity at least twice daily on workdays; inspections for moribund or dead animals were conducted twice daily from Monday through Friday, and once a day on weekends and holidays.

Results: There was one death during the 12-month study. The animal, a male in the 12,000-ppm group, died spontaneously without having exhibited any previous clinical signs. Necropsy showed that death was caused by a tracheal obstruction.

No treatment-related signs of toxicity or clinical symptoms were noted in the dogs treated with the test article. The most common finding, thought not to be attributed to treatment, was sporadic vomiting among single animals in the control and dosed groups. Two females (one control group, one 14,000-ppm group) vomited nearly daily throughout the study. One male in the control group developed demodicosis, for which it was treated. One male in the 4000-ppm group, from December 17, 1985, to December 31, 1985, was very weak, showed abdominal or lateral position, weakness of the rear limbs, relieving posture of the right front limb, and a rise in body temperature, as well as diarrhea, but recovered by December 30, 1985. One dog in the 12,000-ppm group showed erythema of the entire ventral surface and sparse fur.

2. Body Weight: Dogs were weighed before initiation of treatment and once each week thereafter.

Results: Table 2 summarizes mean body weight data at selected intervals. The mean body weights of dogs treated at all dose levels tended to be below those determined for the respective male and female control groups. Significant decreases ($p < 0.05$ at week 10 and $p < 0.01$ from week 12 to the end of the study) were noted in male dogs treated with 12,000 ppm of test material.

TABLE 2. Mean Body Weight at Selected Intervals in Dogs Fed Quinclorac (Reg. No. 150 732)[a]

Dietary Level (ppm)	Mean Body Weight (kg ± S.D.) at Study Week: 0	13	26	52
		Males		
0	8.8 ± 1.0	10.5 ± 0.6	11.3 ± 0.6	11.2 ± 0.7
1,000	8.7 ± 1.2	9.6 ± 1.3	10.7 ± 1.5	10.4 ± 1.1
4,000	8.7 ± 1.1	9.8 ± 0.8	10.8 ± 0.9	10.0 ± 0.8
12,000	8.6 ± 1.2	8.5 ± 1.3**	9.0 ± 1.3**	8.3 ± 1.2**
		Females		
0	9.0 ± 1.4	10.1 ± 1.6	10.8 ± 1.4	10.9 ± 1.3
1,000	9.0 ± 1.2	10.0 ± 1.3	10.5 ± 1.5	10.4 ± 1.7
4,000	8.6 ± 1.4	9.9 ± 1.2	10.7 ± 1.4	10.3 ± 1.5
12,000	8.9 ± 1.2	8.7 ± 0.8	9.3 ± 0.9	9.1 ± 0.7

[a]Data were extracted from study No. 88/0029, pages 152 through 165

**Significantly different from control value at $p < 0.01$.

Mean body weight gains at selected intervals are summarized in Table 3. Mean body weight gains were lower in all treated groups relative to the controls. Statistically significant ($p < 0.01$) decreases were observed from day 7 through study termination in both males and females administered 12,000 ppm of test material. Significant ($p < 0.05$) decreases in body weight gains also were observed sporadically at weeks 3 through 13 for males administered 1,000 ppm of the test material. During the 12-month study period, the male and female dogs of the control group gained weight by an average of 2.3 (27%) and 2.0 kg (21%), respectively. Male dogs in the 12,000-ppm dose group lost 0.1 kg (-1%), whereas female dogs gained only 0.1 kg (1%).

3. Food Consumption and Compound Intake: Feed consumption was measured daily. All animals were weighed once weekly. Food efficiency was calculated for each test group at weekly intervals on the basis of body weight changes and the total amount of food consumed during the weekly interval. Compound intake was calculated weekly for individual animals as mg/kg body weight/day based on nominal dose levels, body weights, and feed consumption.

   Results: Throughout the study, most animals consumed the total amount of feed offered per day. Food efficiency data are summarized in Table 4. Food efficiency for individual intervals varied considerably within a group and between separate groups. When evaluated over the entire duration of the study, food efficiency was clearly less in male and female dogs of the 12,000-ppm test group and was associated with the treatment-related adverse effect on body weight change at this dose level. Food efficiency data for the 1000- and 4000-ppm groups were comparable to the controls. The mean test substance intake values for the 1000-, 4000-, and 12,000-ppm dose level groups were 34.1 ± 3.6, 141.5 ± 11.4, and 512.9 ± 71.8 mg/kg body weight for males and 34.5 ± 5.9, 140.3 ± 21.2, and 469.3 ± 32.1 mg/kg body weight for females, respectively.

4. Ophthalmological Examinations: Ophthalmological examinations were conducted for each dog prior to study initiation, after about 6 months, and at the end of the administration period.

   Results: One male dog of the high-dose group showed opacity of the cornea, as did one control female dog, toward the end of the study. These findings were considered incidental since they were not dose related and were of low degrees of severity.

TABLE 3. Mean Body Weight Gain (kg ± S.D.) at Selected Intervals in Dogs Fed Quinclorac (Reg. No. 150 732)[a]

Dietary Level (ppm)	Mean Body Weight Changes (kg/dog/week) During Weeks: 0-13	0-26	0-52
	Males		
0	1.7 ± 0.6	2.5 ± 0.8	2.3 ± 1.0
1,000	0.9 ± 0.5*	2.0 ± 0.7	1.7 ± 0.6
4,000	1.1 ± 0.5	2.1 ± 0.8	1.3 ± 1.1
12,000	-0.2 ± 0.7**	0.4 ± 0.7**	-0.1 ± 0.7**
	Females		
0	1.2 ± 0.4	1.8 ± 0.4	2.0 ± 0.5
1,000	1.1 ± 0.5	1.5 ± 0.8	1.4 ± 0.9
4,000	1.1 ± 0.2	1.9 ± 0.3	1.5 ± 0.4
12,000	-0.3 ± 0.6**	0.3 ± 0.5**	0.1 ± 0.8**

[a]Data were extracted from study No. 88/0029, pages 166 through 179.

*Significantly different from control value at $p < 0.05$.

**Significantly different from control value at $p < 0.01$.

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TABLE 4. Mean Food Efficiency at Selected Intervals in Dogs Fed Quinclorac (Reg. No. 150 732)[a]

Dietary Level (ppm)	Food Efficiency at Study Weeks[b]: 1-4	12-16	28-32	48-52	1-52
			Males		
0	10.2	6.1	-1.0	-1.0	1.9
1000	3.1	7.2	-1.0	-2.0	1.3
4000	5.1	4.1	-1.0	-3.1	1.0
12,000	-2.4	3.1	-2.0	-2.0	-0.3
			Females		
0	3.2	6.1	-2.0	2.0	1.2
1000	3.1	5.1	0	-1.0	1.1
4000	3.1	4.1	-3.1	2.0	1.1
12,000	-4.3	2.1	-1.0	1.0	-0.1

[a]Data were extracted from Study No. 88-0029, pages 180 and 181.

[b]Food efficiency was calculated using the formula $\frac{BW_{x+n} - BW_x}{F_x} \times 7.0$

BW_{x+n} = Mean body weight on day x + 28** (in kg)

BW_x = Mean body weight on day x (in kg)

F_x = Mean food consumption from days 0 to 27, 28 to 55, 56 to 83, etc. (in kg), divided by 2 to account for water added to the dry feed.

**Because of holiday, in weeks 36-40, BW_{x+n} was mean body weight on day x + 27, and in weeks 40-44, BW_{x+n} was mean body weight on day x + 29.

5. Hematology and Clinical Chemistry: Blood samples were collected from all dogs via the vena cephalica antebrachii 1 week prior to study initiation and about 13, 26, and 52 weeks after initiation of the study for determination of hematological clinical chemistry values. The CHECKED (X) parameters were examined:

a. Hematology:

X Hematocrit (HCT)†
X Hemoglobin (HGB)†
X Leukocyte count (WBC)†
X Erythrocyte count (RBC)†
X Platelet count†
X Reticulocyte count (RETIC)
Red cell morphology
X Differential blood count
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)
Coagulation: thromboplastin time (PT)

Results: Table 5 summarizes selected hematology data at specific study periods for dogs fed quinclorac (Reg. No. 150 732) for 12 months. Several treatment-related changes in hematology values were noted. In both male and female dogs fed 12,000 ppm of test material, there were significant ($p < 0.01$) reductions in hemoglobin concentration, erythrocyte count, hematocrit, mean corpuscular hemoglobin (MCH) values, and mean corpuscular volume (MCV). In females receiving 4000 ppm, hemoglobin concentration, erythrocyte counts, and hematocrit values were also significantly reduced ($p < 0.05$), but only at the 26-week interval; one male receiving 4000 ppm had decreases in HGB, RBC, and HCT at 52 weeks but the group mean value was not significantly lower than in controls. There were no changes in the 1000- and 4000-ppm groups that could be clearly attributed to the administration of test substance. The study author attributed the anemic process, i.e. reduced hemoglobin concentrations, MCH values, and diminished mean cell volume, to a disturbed synthesis of heme and hemoglobin.

†Recommended by Subdivision F (November 1984) Guidelines.

TABLE 5. Selected Hematology Data (Mean ± S.E.) in Dogs Fed Quinclorac (Reg. No. 150 732)

Parameter/ Dietary Level	Mean Value (± S.E.) at Week: Males 13	Males 26	Males 52	Females 13	Females 26	Females 52
Hemoglobin (mmol/L)						
0	9.66 ± 0.16	10.12 ± 0.24	10.36 ± 0.13	9.79 ± 0.22	10.50 ± 0.31	10.23 ± [illegible]
1,000	9.33 ± 0.37	10.04 ± 0.40	10.19 ± 0.25	9.39 ± 0.31	9.76 ± 0.36	9.78 ± [illegible]
4,000	9.16 ± 0.26	10.00 ± 0.31	9.96 ± 0.43	10.05 ± 0.29	9.49 ± 0.16*	10.25 ± [illegible]
12,000	7.40 ± 0.17**	8.25 ± 0.29**	8.63 ± 0.31**	8.52 ± 0.48*	8.73 ± 0.21**	8.74 ± [illegible]*
Erythrocyte count (Tera/L)						
0	6.60 ± 0.14	6.78 ± 0.18	6.96 ± 0.10	6.62 ± 0.13	7.10 ± 0.16	6.83 ± [illegible]
1,000	6.29 ± 0.25	6.75 ± 0.24	6.89 ± 0.17	6.38 ± 0.19	6.63 ± 0.20	6.65 ± [illegible]
4,000	6.28 ± 0.20	6.83 ± 0.24	6.81 ± 0.29	6.88 ± 0.25	6.47 ± 0.15*	6.93 ± [illegible]
12,000	5.28 ± 0.10**	5.82 ± 0.18**	6.04 ± 0.22*	6.10 ± 0.32	6.22 ± 0.17**	6.22 ± [illegible]
Hematocrit (%)						
0	0.46 ± 0.01	0.48 ± 0.01	0.49 ± 0.01	0.47 ± 0.01	0.51 ± 0.02	0.49 ± [illegible]
1,000	0.44 ± 0.02	0.48 ± 0.02	0.49 ± 0.01	0.45 ± 0.01	0.47 ± 0.02	0.47 ± [illegible]
4,000	0.44 ± 0.01	0.48 ± 0.02	0.48 ± 0.02	0.48 ± 0.01	0.45 ± 0.01*	0.49 ± [illegible]
12,000	0.36 ± 0.01**	0.40 ± 0.01**	0.42 ± 0.01**	0.41 ± 0.02	0.42 ± 0.01**	0.42 ± [illegible]*
Mean Hemoglobin Content per Erythrocyte (fmol)						
0	1.46 ± 0.01	1.49 ± 0.01	1.49 ± 0.01	1.48 ± 0.01	1.48 ± 0.01	1.50 ± [illegible]
1,000	1.48 ± 0.01	1.49 ± 0.02	1.48 ± 0.01	1.47 ± 0.02	1.47 ± 0.02	1.47 ± [illegible]
4,000	1.46 ± 0.01	1.46 ± 0.01	1.46 ± 0.01	1.46 ± 0.02	1.47 ± 0.01	1.48 ± [illegible]
12,000	1.40 ± 0.01**	1.41 ± 0.01**	1.43 ± 0.02*	1.39 ± 0.02**	1.40 ± 0.01**	1.41 ± [illegible]**
Mean Corpuscular Volume (fL)						
0	69.7 ± 0.47	70.5 ± 0.22	70.93 ± 0.45	70.23 ± 0.58	71.47 ± 0.64	71.63 ± [illegible]
1,000	69.8 ± 0.58	70.4 ± 0.70	70.65 ± 0.35	70.20 ± 0.77	70.48 ± 0.81	70.22 ± [illegible]
4,000	69.3 ± 0.54	69.6 ± 0.70	69.90 ± 0.38	69.45 ± 0.89	69.98 ± 0.62	70.35 ± [illegible]
12,000	67.3 ± 0.55**	67.9 ± 0.70**	68.78 ± 0.96	67.07 ± 1.00*	67.13 ± 0.64**	68.23 ± [illegible]**

*Significantly different from control value at p <0.05.

**Significantly different from control value at p <0.01.

b. Clinical Chemistry:

	Electrolytes		Other
X	Calcium†	X	Albumin†
X	Chloride†		Albumin/globulin ratio
	Magnesium†	X	Blood creatinine†
X	Phosphorus†		Blood urea nitrogen†
X	Potassium†	X	Cholesterol†
X	Sodium†	X	Globulins
		X	Glucose†
	Enzymes	X	Total bilirubin†
X	Alkaline phosphatase (ALP)		Direct bilirubin
	Cholinesterase	X	Total protein†
	Creatine phosphokinase†	X	Triglycerides
	Lactic acid dehydrogenase	X	Urea
X	Serum alanine aminotransferase (SGPT)†	X	Partial thromboplastin time
X	Serum aspartate aminotransferase (SGOT)†		
	Gamma glutamyltransferase (GGT)		

Results: Selected clinical chemistry data are summarized in Table 6. Following administration of 12,000 ppm of test substance, decreases in creatinine, urea, total protein, albumin, calcium, triglycerides, total bilirubin, alkaline phosphatase, and glutamate pyruvate transaminase (SGPT) values were noted in the plasma of both sexes. Significant ($p < 0.01$) changes were noted only for creatinine, calcium, and albumin. At the 4000-ppm level, a decrease in creatinine, urea, and protein values was noted in both sexes, whereas there was a decrease in the calcium level value in females and a reduction in alkaline phosphatase activity in males. Changes in other parameters were considered incidental. There were no changes in the 1000-ppm group that could be related to treatment.

6. Urinalysis: Individual urine samples were collected overnight from all dogs 1 week prior to initiation of the study and about 13, 26, and 52 weeks after beginning administration of test compound. The CHECKED (X) parameters were examined:

	Appearance†	X	Glucose†
X	Volume†	X	Ketones
X	Specific gravity†	X	Bilirubin†
X	pH	X	Blood†
X	Sediment (microscopic)†		Nitrate
X	Protein†	X	Urobilinogen
		X	Nitrite

†Recommended by Subdivision F (November 1984) Guidelines.

TABLE 6. Selected Clinical Chemistry Data (Mean ± Standard Error) in Dogs Fed Quinclorac (Reg. No. 150 732)

Parameter/ Dietary Level (ppm)	Mean Value (± Standard Error) in Dogs Fed Reg. No. 150 732							
	Males				Females			
	0	13	26	52	0	13	26	52
Total Bilirubin (µmol/L)								
0	2.63 ± 0.39	3.55 ± 0.52	2.49 ± 0.30	2.86 ± 0.61	3.29 ± 0.35	3.46 ± 0.59	2.20 ± 0.35	2.44 ± 0.22
1000	2.70 ± 0.13	3.74 ± 0.39	2.71 ± 0.24	2.29 ± 0.36	2.98 ± 0.34	3.59 ± 1.48	2.39 ± 0.15	2.42 ± 0.13
40	2.27 ± 0.32	2.09 ± 0.30*	1.72 ± 0.24	1.25 ± 0.25*	3.17 ± 0.38	3.14 ± 0.52	1.95 ± 0.41	2.30 ± 0.38
12,000	3.12 ± 0.51	2.40 ± 0.48	1.22 ± 0.26*	1.18 ± 0.33	2.93 ± 0.13	2.44 ± 0.29	1.21 ± 0.22*	1.48 ± 0.12**
Creatinine (µmol/L)								
0	76.02 ± 2.47	86.34 ± 2.30	86.28 ± 4.52	86.16 ± 4.14	83.76 ± 4.41	84.09 ± 2.87	86.44 ± 1.80	85.52 ± 3.04
1000	75.72 ± 2.47	80.01 ± 1.82	80.71 ± 2.02	78.28 ± 3.27	72.21 ± 3.19	85.45 ± 3.67	79.15 ± 2.38*	80.32 ± 3.78
4000	71.69 ± 2.84	77.49 ± 1.74*	75.41 ± 1.93	69.74 ± 3.07**	78.76 ± 4.03	81.15 ± 3.51	78.00 ± 2.87*	74.58 ± 3.01*
12,000	70.33 ± 2.19	66.38 ± 3.15**	58.63 ± 1.53**	53.10 ± 1.35**	79.44 ± 5.19	71.60 ± 1.82**	65.77 ± 2.52**	61.41 ± 1.87**
Calcium (mmol/L)								
0	2.88 ± 0.04	2.82 ± 0.03	2.77 ± 0.04	2.64 ± 0.02	2.86 ± 0.03	2.80 ± 0.03	2.76 ± 0.03	2.80 ± 0.02
1000	2.87 ± 0.03	2.75 ± 0.04	2.72 ± 0.04	2.61 ± 0.02	2.87 ± 0.03	2.70 ± 0.02**	2.78 ± 0.05	2.79 ± 0.04
4000	2.86 ± 0.05	2.75 ± 0.04	2.73 ± 0.07	2.55 ± 0.04	2.85 ± 0.03	2.73 ± 0.03	2.71 ± 0.04	2.71 ± 0.03*
12,000	2.77 ± 0.03	2.66 ± 0.05*	2.51 ± 0.05*	2.49 ± 0.06*	2.82 ± 0.01	2.68 ± 0.02**	2.64 ± 0.04*	2.66 ± 0.02**
Albumin (g/L)								
0	36.67 ± 0.75	38.57 ± 0.69	39.93 ± 0.45	38.73 ± 0.88	39.20 ± 0.51	41.10 ± 0.68	41.15 ± 1.11	41.00 ± 0.53
1000	37.98 ± 0.98	38.30 ± 0.96	40.37 ± 0.85	40.02 ± 0.31	38.40 ± 0.65	39.65 ± 0.99	39.95 ± 1.34	40.80 ± 0.89
4000	36.65 ± 0.98	37.80 ± 0.76	39.12 ± 0.91	38.07 ± 1.06	39.50 ± 0.47	40.30 ± 0.45	39.60 ± 0.64	40.32 ± 0.93
12,000	34.45 ± 0.27	34.03 ± 1.22**	36.08 ± 0.66**	35.82 ± 0.43*	37.77 ± 1.00	36.58 ± 0.91**	35.42 ± 0.71**	36.35 ± 1.43*

*Significantly different from control value at $p < 0.05$.

**Significantly different from control value at $p < 0.01$.

Results: No effects of treatment with quinclorac (Reg. No. 150 732) on urinalysis parameters were seen.

7. Sacrifice and Pathology: All surviving animals that were sacrificed on schedule and the single male that died spontaneously during the study were subject to complete necropsy and gross pathological examination. The CHECKED (X) tissues were collected and fixed. In addition, the (XX) organs were weighed:

Digestive System	Cardiovasc./Hemat.	Neurologic
Tongue	X Aorta[1]	XX Brain
X Salivary glands[1]	X Heart[1]	X Peripheral nerve (sciatic nerve)[1]
X Esophagus[1]	X Bone marrow[1]	X Spinal cord (3 levels)
X Stomach[1]	X Lymph nodes[1]	X Pituitary[1]
X Duodenum[1]	X Spleen	X Eyes (optic nerve)[1]
X Jejunum[1]	X Thymus	
X Ileum[1]		
X Cecum[1]		
X Colon[1]		
X Rectum	Urogenital	Glandular
XX Liver[1]	XX Kidneys[1]	XX Adrenals[1]
X Gallbladder[1]	X Urinary bladder[1]	Lacrimal gland
X Pancreas[1]	XX Testes[1]	X Mammary gland[1]
	Epididymides	XX Thyroids[1]
	X Prostate	X Parathyroids[1]
	Seminal vesicle	Harderian glands
Respiratory	XX Ovaries	
X Trachea[1]	X Uterus	
X Lung[1]		
		Other
		X Bone (sternum and femur)[1]
		X Skeletal muscle[1]
		X Skin
		X All gross lesions and masses

Results:

a. Organ Weights: Table 7 presents mean organ weight data for liver, kidney, brain, adrenals, and thyroids. The absolute liver weight of female dogs in the 12,000-ppm group was statistically significantly ($p < 0.01$) increased by about 31%. Absolute liver weight in males

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[1]Recommended by Subdivision F (November 1984) Guidelines.

TABLE 7. Mean Organ Weights (g ± S.D.) and Mean Organ-to-Body Weight Ratios (% ± S.D.) in Dogs Fed Quinclorac (Reg. No. 150 732)[a]

Dietary Level (ppm)	Males		Females	
	g	(%)[b]	g	(%)
		Liver		
0	365 ± 70	3.26 ± 0.49	360 ± 63	3.32 ± 0.48
1,000	383 ± 72	3.69 ± 0.67	412 ± 72	3.99 ± 0.62*
4,000	350 ± 41	3.52 ± 0.57	403 ± 39	3.96 ± 0.41*
12,000	406 ± 42	4.90 ± 0.28**	473 ± 60**	5.22 ± 0.50**
		Kidney		
0	52.3 ± 4.6	0.47 ± 0.05	52.5 ± 7.8	0.49 ± 0.06
1,000	51.6 ± 3.2	0.50 ± 0.05	54.2 ± 6.8	0.53 ± 0.07
4,000	56.5 ± 8.3	0.56 ± 0.05**	55.6 ± 5.0	0.55 ± 0.05
12,000	60.1 ± 6.9	0.73 ± 0.06**	60.3 ± 6.1	0.66 ± 0.04**
		Brain		
0	80.5 ± 4.1	0.72 ± 0.06	75.3 ± 6.8	0.70 ± 0.05
1,000	78.7 ± 2.8	0.76 ± 0.08	77.3 ± 6.0	0.76 ± 0.10
4,000	80.9 ± 4.1	0.81 ± 0.06	76.5 ± 2.7	0.76 ± 0.10
12,000	84.6 ± 4.4	1.03 ± 0.12**	74.0 ± 4.5	0.82 ± 0.05*
		Adrenals		
0	1.08 ± 0.14	0.0097 ± 0.0007	1.24 ± 0.31	0.0116 ± 0.003
1,000	1.07 ± 0.18	0.0103 ± 0.0016	1.51 ± 0.27	0.0148 ± 0.003
4,000	1.14 ± 0.22	0.0116 ± 0.0027	1.49 ± 0.31	0.0148 ± 0.00[illegible]
12,000	1.11 ± 0.13	0.0135 ± 0.0021**	1.34 ± 0.13	0.0148 ± 0.001
		Thyroid		
0	0.83 ± 0.24	0.0074 ± 0.002	0.86 ± 0.24	0.0078 ± 0.00[illegible]
1,000	0.86 ± 0.15	0.0082 ± 0.001	1.02 ± 0.28	0.0097 ± 0.00[illegible]
4,000	0.84 ± 0.17	0.0084 ± 0.002	0.88 ± 0.23	0.0085 ± 0.00[illegible]
12,000	0.85 ± 0.15	0.0103 ± 0.002*	1.11 ± 0.21	0.0123 ± 0.00[illegible]**

[a]Data were extracted from study No. 88/0029, pages 230 through 233.

[b]Percentage of body weights.

*Significantly different from control value at $p < 0.05$.

**Significantly different from control value at $p < 0.01$.

of this group increased about 11%, but were not statistically significant. Relative (to body weight) liver weight of males and females of the 12,000-ppm group also were significantly increased (approximately 50% for males and 57% for females). There were no histopathologic correlates to the liver weight gains. Relative liver weights were also significantly ($p < 0.05$) increased in females of the 1000- and 4000-ppm groups.

Kidney weights tended to be increased at 4,000 ppm and 12,000 ppm in a dose-related manner, but the increases were not statistically significant; at the 12,000-ppm dose the weights were about 15% greater than in the controls. The relative kidney weights of male and female dogs in the 12,000-ppm test group were significantly ($p < 0.01$) increased (by about 55% in males and 35% in females). Relative kidney weight also was significantly ($p < 0.01$) increased by about 19% in females of the 4000-ppm group.

Statistically significant ($p < 0.01$ or 0.05) increases in relative brain, adrenals, and thyroid weights were observed in animals treated with 12,000 ppm of test material; however, the absolute weights were comparable in the control and dosed groups. The author did not consider the changes to be of biological importance.

b. Gross Pathology: Gross pathology examination revealed only incidental spontaneous findings, including the following: two dogs with small prostrate; lungs that were dark red or had dark red areas in seven dogs; two dogs with sparse hair or reddened skin; and in the dog that died, a trachea obstructed by clumps of food.

c. Microscopic Pathology: Table 8 summarizes the incidence of frequently occurring nonneoplastic lesions in dogs fed quinclorac (Reg. No. 150 732) for 12 months. Histopathological findings in the liver were limited to an increase in focal mononuclear infiltrates in the 12,000-ppm animals. Single cell necrosis was also seen in two dogs of this test group. Hydropic degeneration of the kidney was seen in two male and female dogs of the 12,000-ppm group. These changes were considered to be treatment related. The other histopathologic findings were of the type and frequency anticipated in this age and breed of dog. No neoplastic lesions were observed.

effects. Similarly, decreases in SGPT and SGOT in 12,000-ppm males and females at 52 weeks and 12,000 ppm females at 52 weeks are not an indication of a toxic effect. Bilirubin tends to increase with a decrease in food consumption and food efficiency or with hemolytic anemia; hence, decreases in bilirubin are not of toxicologic importance but may indicate that anemia is not of the hemolytic type. The above findings indicate no effect of major importance; since there were no histologic correlates to the clinical chemical changes, they are of doubtful importance.

The reviewers agree with the study author that the clinical chemistry findings were caused by the adverse effect on food efficiency, since most of the parameters affected are dependent, more or less, on the nutritional state of the animal. Animals in the 12,000-ppm group were in a poorer state of health than those of the other groups, as evidenced by their significantly reduced body weight gains.

Significant increases in absolute ($p < 0.01$ for females) and relative liver weights ($p < 0.01$ for both males and females) were observed at 12,000 ppm. Relative liver weights also were significantly increased ($p < 0.05$) in females of the 4000- and 1000-ppm groups. Correlating histopathologic changes in the liver were lacking. Findings in the liver were limited to an increase in focal mononuclear infiltration and to single cell necrosis in two dogs in the 12,000 ppm group. The mean absolute kidney weights increased 15% above controls in females and males receiving 12,000 ppm and 6 to 8% at 4000 ppm, but the increases at both doses were not statistically significant. An apparent dose-related trend for an increase in kidney-to-body weight ratios was seen in both sexes and there was a marked and significant increase at the highest dose. The effect at the 12,000 ppm may correlate with the hydropic degeneration of the kidney seen in two males and two females at this dose.

The reviewers conclude that based on the reduced body weights and body weight gains, adverse effect on food efficiency, hematological and clinical chemistry values, increased liver and kidney weights, and hydropic degeneration in the kidney in both sexes receiving 12,000 ppm. The no-observed-effect level (NOEL) is 4,000 ppm and the lowest-observed-effect level (LOEL) is 12,000 ppm.

The following range-finding study was examined and conclusions drawn. A DER will not be completed for the study.

Title: Report on the Study of the Toxicity of Reg. No. 150 732 in Beagle Dogs After 4 Week Administration in the Diet (BASF #85/0234; 11/18/83) - MRID #410635-20

Summary - Dogs were fed 0, 1000, 3000, 9000 and 27000 ppm of Reg. No. 150 732 in the diet for 4 weeks. At 9000 ppm there was a decrease in alkaline phosphatase. At 27000 ppm there was decreased food consumption and body weight, vomiting, decrease in alkaline phosphatase, chronic focal or multifocal interstitial nephritis, decreased testes weight, focal dilation of kidney tubules with flattening of the epithelium and fatty degeneration of the glomeruli.

NOEL = 3000 ppm (75 mg/kg/day)
LEL = 9000 ppm (225 mg/kg/day)
Core - Supplementary

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

EPA No.: 68D80056
DYNAMAC No.: 275-A
TASK No.: 2-75A
May 3, 1990

DATA EVALUATION RECORD

QUINCLORAC

Oncogenicity Feeding Study in Mice

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Robert J. Weir

Date: May 4, 1990

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EPA No.: 68D80056
DYNAMAC No.: 275-A
TASK No.: 2-75A
May 3, 1990

DATA EVALUATION RECORD

QUINCLORAC

Oncogenicity Feeding Study in Mice

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DATA EVALUATION RECORD

GUIDELINE § 83-2

STUDY TYPE: Oncogenicity feeding study in mice.

MRID NUMBER: 410635-23.

TEST MATERIAL: Quinclorac (Reg. No. 150 732).

SYNONYMS: BASF 514 COH; 3,7-dichloro-8-quinolinecarboxylic acid.

STUDY NUMBER: 80S0282/8520; BASF# 88/5114.

SPONSOR: BASF Corporation, Chemicals Division, Agricultural Chemicals, Parsippany, NJ 07054.

TESTING FACILITY: BASF Aktiengesellschaft, Department of Toxicology, D-6700 Ludwigshafen/Rhein, Federal Republic of Germany.

TITLE OF REPORT: Study of the Potential Carcinogenic Effect of Quinclorac (Reg. No. 150 732) in Mice--Dietary Administration for 78 Weeks.

AUTHOR: Schilling, K.

REPORT ISSUED: September 14, 1988.

CONCLUSIONS: Quinclorac was fed to male and female B6C3F1/CrlBr mice at dietary levels of 0, 250, 1000, 4000, or 8000 ppm for 6 months or 78 weeks. At the end of 78 weeks, body weights in males and females receiving 8000 ppm were significantly lower than controls by 9.6% and 7.4%, respectively. Body weights in males and females receiving 1000, 4000, or 8000 ppm for 78 weeks were significantly lower than controls (7.9 to 15.9% for males; 14.3 to 17.9% for females). Treatment-related body weight reductions compared with controls were also noted in satellite males and females receiving 4000 or 8000 ppm for 6 months. Absolute liver weights were significantly reduced in male and female mice receiving 8000 ppm for 78 weeks, but there was no effect on liver-to-body weight ratio. Absolute kidney weights were decreased in males receiving 1000, 4000, or 8000 ppm and in females receiving 4000 or 8000 ppm for 78 weeks. Relative kidney weights were decreased in males receiving 1000, 4000, or 8000 ppm for 78 weeks. Dose-related increases in relative brain weights were seen in males and females treated orally with quinclorac for 78 weeks. Absolute liver weights were also reduced in males receiving 4000 or 8000 ppm for 6 months, while absolute kidney weights were reduced in all treated males. A slight decrease in hematocrit values was noted in males and females receiving 8000 ppm for 6 months, but not 78 weeks. Effects on other hematological parameters were not of biological significance. There were no increases in neoplastic findings related to dosing with Quinclorac. There was no effect of dosing on mortality, food consumption, or clinical signs.

The LOEL is 1000 ppm based on effects on body weight. The NOEL is 250 ppm. A maximum tolerated dose (MTD) was approached based on decreased body weights in males and females receiving 8000 ppm.

Classification:* This study satisfies the requirements for an oncogenicity study (83-2) in the mouse.

*Core - Guideline

A. MATERIALS:

1. Test Compound: Quinclorac (Reg. No. 150 732); description: colorless crystals; batch and purity:

Batch No.	Purity (%)
III N55	97.38
III 2N57*	98.29

*This batch was fed to the animals from the third week in March 1986 onward. The study was initiated in September 1985.

2. Test Animals: Species: Mouse; strain; B6C3F1/CrlBr; age: 43-44 days (main study), 40 days (supplementary study); weight: males--19.0 to 23.0 g (main study), 19.7 to 24.5 (supplementary study), females--16.0 to 20.0 g (main study) and 16.8 to 20.4 g (supplementary study); source: Charles River Breeding Laboratory, Wilmington, MA.

B. STUDY DESIGN:

1. Animal Assignment: Animals were acclimated to laboratory conditions for 4 to 5 days (main study) or 8 days (supplementary study) and were randomly assigned to the following test groups on the basis of their weights:

		Main Study				Supplementary Study			
		Main Group (78 weeks)		Satellite Group[a] (6 months)		Main Group (78 weeks)		Satellite Group[a] (6 months)	
Test Group	Dose in Diet (ppm)	Males	Females	Males	Females	Males	Females	Males	Females
1	0	50	50	10	10	50	50	10	10
2	250[b]	--		--	--	50	50	10	10
3	1000	50	50	10	10	--	--	--	--
4	4000	50	50	10	10	--	--	--	--
5	8000	50	50	10	10	--	--	--	--

[a]The use of satellite groups was intended to determine the overall toxicity of the test substance, such as its effect on hematological and clinical chemistry parameters, clinical examinations, and pathology.

[b]The dose of 250 ppm was administered to mice in a supplementary study to determine a no-effect level below 1000 ppm. The supplementary study was initiated about 15 months after the main study.

Dose levels were selected on the basis of the results of previous toxicity studies in mice and rats. These studies were not available for review. In a 28-day study, mice were administered 1,000, 4,000, 8,000, or 16,000 ppm test substance in the diet. No effects were seen at doses up to 8000 ppm. A loss in body weight was observed in mice receiving 16,000 ppm. Pathology revealed that the absolute kidney weights were decreased in both sexes and the absolute liver weights were increased in the male animals at the high dose. In a 90-day study, rats were administered 1,000, 4,000, or 12,000 ppm. Body weight and food consumption were reduced at the highest dose in both sexes. The serum activity of glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase was increased in males receiving 12,000 ppm; hemoglobin, hematocrit, mean corpuscular hemoglobin were reduced in females receiving 12,000 ppm. In previous range-finding studies, body weight and food consumption were reduced at 15,000 and 30,000 ppm in both sexes and several clinical chemistry parameters were

affected; nephropathy was observed in both sexes at 15,000 and 30,000 ppm, and cloudy swelling of hepatocytes was observed in 30,000-ppm males and females.

In the chronic mouse study, 8000 ppm was selected as the highest dose level, since it was expected that there would be marginal signs of toxicity with this dose, but no effect on the normal lifespan. A dose of 1000 ppm was initially chosen as the lowest dose level, but a subsequent dose of 250 ppm was tested in a supplementary study to establish a no-effect level.

In the present study, mice were housed singly in cages in a room with temperature and humidity controls set at 20-24°C and 30-70%, respectively, and with a 12-hour light/dark cycle.

2. Diet Preparation: The test substance was thoroughly mixed with a small portion of the feed, and subsequently mixed using a Bosch mixer. This premix was then adjusted to the required concentration by adding the appropriate amount of feed and was mixed in a laboratory mixer for about 10 minutes. Diets containing quinclorac were prepared at least once monthly. The stability of the test substance in the diet for a period of 30 days and homogeneity were verified in this and previous studies. Concentrations of the test substances in diets were analyzed at 3-month intervals.

   Results. Analysis of diets at levels of 100, 300, 400, 1,600, 5,000, 6,400, 15,000 and 30,000 ppm indicated homogeneity from 76.2 to 118% of the target level. However, values were generally within 10% of the nominal values. Previous data showed that the test compound was stable in the diet over a period of 30 days. Table 1 summarizes data on nominal and analyzed dietary levels of quinclorac. Values for test compound were generally in agreement with nominal values. The percentage deviation from nominal values, determined at the beginning of the study and then at three-monthly intervals, were -2.8% to 4.4%, -5.8% to 10.5%, -2.3% to 16.8%, 0.79% to 5.8%, and -8.6% to 8.9% at dose levels of 250, 1,000, 4,000, 8,000, and 12,000 ppm, respectively.

3. Food and Water Consumption: Animals received food (ground Kliba 343 rat/mouse/hamster "A" maintenance diet) and water ad libitum.

4. Statistics: In the statistical evaluation of the study, means and standard deviation of data on food consumption, body weight, compound intake, food efficiency, and

TABLE 1. Dietary Levels of Quinclorac

Nominal Level (ppm)	Analyzed Level (ppm)	(range)
250	252.0 ± 12.7	243.0 - 261.0
1,000	1026.9 ± 52.7	942.5 - 1105.0
4,000	4120.6 ± 266.1	3888.5 - 4672.0
8,000	8188.5 ± 208.2	8063.5 - 8465.0
12,000	12006.9 ± 734.9	10971.0 - 13070.0

hematology were calculated for the animals in each test group. Body weight and hematology (excepting the differential blood count) were examined for statistical significance of variance (ANOVA) followed by Dunnett's test.

For the evaluation of histopathological findings (including tumors), Fisher's exact probability test with the exact test for trend was applied to the data of all groups, even though only lungs, livers, and kidneys of all low- and mid-dose mice were evaluated histopathologically. Therefore, only those statistical deviations with possible biological relevance were confirmed by a modified Kruskal-Wallis rank test.

5. Quality Assurance: A quality assurance statement was signed and dated September 14, 1988. An updated GLP compliance statement was also present.

C. METHODS AND RESULTS:

1. Observations: The animals were examined daily for any evident signs of toxicity. In addition to the general daily observation, each animal was subjected once a week to clinical examination, including palpation for tissue masses. Any abnormalities and changes were recorded for each animal. A check was made at least once daily for any dead or moribund animals.

   Results: No clinical signs attributable to treatment were observed during the study period. The mortality of the animals was not affected by the administration of quinclorac. Survival rates at 78 weeks were 98 to 100% in the male groups and 94 to 100% in the female groups in the main study. In the supplementary study, 78-week survival was between 90 and 93% in all groups. The number of animals that were prematurely sacrificed in a moribund state was about the same in the control and test groups.

2. Body Weight: Mice were weighed once a week during the first 14 weeks and every 4 weeks throughout the remainder of the test period. The body weight for the randomization of the animals was determined one day prior to the start of the administration period.

   Results: Table 2 summarizes data on mean body weights of mice in the main study at selected intervals. A dose-related significant body weight reduction compared with the control was observed in all dose groups. Mean body weights were significantly ($p \leq 0.01$) lower than controls in males and females receiving 4000 and 8000 ppm at all evaluated intervals up to and including week 78. At termination, mean body weights in males receiving 4000 and 8000 ppm were

TABLE 2. Mean Body Weight at Selected Intervals in Mice Fed Quinclorac for 78 Weeks

Dietary Level (ppm)	Mean Body Weights (g ± S.D.) at Week: 0	13	26	38	50	78
			Males			
0	21.3 ± 0.8	29.1 ± 2.2	32.0 ± 2.8	35.3 ± 3.4	35.4 ± 3.8	34.0 ± 3.8
1000	21.2 ± 0.7	28.4 ± 1.7	31.9 ± 2.4	34.3 ± 3.2	34.0 ± 3.2*	31.3 ± 3.1**
4000	21.1 ± 0.8	26.9 ± 1.2**	29.4 ± 2.0**	31.7 ± 2.6**	31.5 ± 2.3**	29.4 ± 2.3**
8000	21.0 ± 0.8	26.3 ± 1.5**	28.8 ± 2.2**	30.0 ± 2.6**	30.1 ± 2.3**	28.6 ± 1.8**
			Females			
0	17.7 ± 0.8	25.7 ± 1.8	28.6 ± 3.0	32.0 ± 4.1	34.8 ± 4.8	33.6 ± 5.0
1000	17.5 ± 0.8	25.0 ± 1.9	27.6 ± 3.1	29.7 ± 4.1**	31.0 ± 4.4**	28.8 ± 4.4**
4000	17.4 ± 0.8	24.0 ± 1.1**	26.9 ± 1.9**	28.8 ± 2.9**	30.1 ± 3.0**	28.5 ± 3.1**
8000	17.4 ± 0.8	23.8 ± 1.4**	26.2 ± 1.9**	27.3 ± 2.7**	28.9 ± 2.6**	27.6 ± 2.6**

*Significantly different from control value, $p \leq 0.05$.

**Significantly different from control value, $p \leq 0.01$.

13.5% and 15.9% lower ($p \leq 0.01$) than controls, respectively; in females receiving the same doses, the body weights were 15.2% and 17.9% lower than controls, respectively. Mean body weights were significantly ($p \leq 0.01$) lower than controls in males receiving 1000 ppm between weeks 50 and 78, whereas mean body weights of females receiving this dose were significantly lower than controls between weeks 30 and 78. At termination, mean body weights in males and females receiving 1000 ppm were 7.9% and 14.3% lower ($p \leq 0.01$) than controls, respectively.

In the 6-month satellite groups (10/sex/group), body weights were similar to those in the main group but the decreases were not significant in females receiving 1000 or 4000 ppm. A significant body weight reduction compared with controls was also noted in males and females receiving 4000 or 8000 ppm for 6 months, and in females receiving 8000 ppm. Mean body weights were significantly ($p < 0.01$) lower than controls in males receiving 8000 ppm (7.7 to 16.1% lower) between weeks 6 and 26, while mean body weights were 4.4 to 8.8% lower ($p < 0.01$) in females receiving this dose between weeks 2 and 12. Mean body weights were also significantly ($p < 0.01$) lower (8.6 to 14.5%) than controls in males receiving 4000 ppm between weeks 9 and 26. Significant reductions in body weights (up to 9%) occurred sporadically in low-dose males. Female mice receiving 1000 or 4000 ppm showed no differences in body weight when compared with the controls.

Male and female mice receiving 250 ppm for 6 months or 78 weeks (supplementary study) did not show any remarkable differences in body weight when compared with the control groups.

3. Food Consumption and Compound Intake: Food consumption of male and female mice was determined once a week, including week 14 of administration, and from then onward every 4 weeks.

   Results: Throughout the study period, and in both the main and supplementary studies, the male and female animals of all dose groups did not show any remarkable differences compared with the control animals with regard to the amount of food consumed daily. Variations, which occurred sporadically in certain test groups, were not considered treatment-related by the study author but rather a reflection of sporadic spilling of food.

4. Ophthalmological Examinations: Ophthalmological examinations were not performed.

5. Hematology and Clinical Chemistry: Blood was collected at 6 months (satellite groups) and 18 months (main groups) from the retroorbital venous plexus of fasted animals or after decapitation. The hematological examinations were carried out in the first 10 surviving animals per test group and sex at the end of the administration period. Additionally, blood smears for differential blood count were prepared from animals in the main study, from those sacrificed intercurrently, and at the end of the administration period from all the surviving animals. Only the control and highest dose groups were evaluated in the main study. The smears of the intermediate dose groups were not evaluated, since assessment of the differential blood counts of the control and the highest dose groups did not reveal any deviations attributable to the test substance administered. At termination of the supplementary study, blood smears were also obtained and evaluated from all surviving animals. Furthermore, blood smears were prepared and evaluated from animals killed in the moribund state during the study. The CHECKED (X) parameters were examined:

a. Hematology:

X Hematocrit (HCT)[1]
X Hemoglobin (HGB)[1]
X Leukocyte count (WBC)[1]
X Erythrocyte count (RBC)[1]
X Platelet count[1]
X Reticulocyte count (RETIC)
X Red cell morphology
X Leukocyte differential count
Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)
Coagulation: thromboplastin time (PT)
X Mean hemoglobin content per erythrocyte
X White cell morphology

Results: A marginal decrease in hematocrit values in both sexes (satellite groups) receiving 8000 ppm for 6 months was noted. In contrast to the satellite groups, no impairment of the hematocrit values in either sex could be detected in the main group in the main study. Consequently, the slight decrease in hematocrit values in the high-dose animals of the satellite group (main study) was considered by the study author to be incidental. Other hematological changes in both satellite and main groups in the main study were considered by the study author to be of little or no biological importance. The administration of 250 ppm to male and female mice over a period of 78 weeks caused no changes attributable to the test substance administered.

[1]Recommended by Subdivision F (November 1984) Guidelines.

b. Clinical Chemistry: Clinical chemistry parameters were not examined.

6. Urinalysis: Urinalyses were not performed.

7. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subjected to gross pathological examination, and the CHECKED (X) tissues were collected for histological examination. In addition, the (XX) organs were weighed:

	Digestive System		Cardiovasc./Hemat.		Neurologic
X	Tongue	X	Aorta[1]	XX	Brain
X	Salivary glands[1]	X	Heart[1]	X	Peripheral nerve (sciatic nerve)[1]
X	Esophagus[1]	X	Bone marrow[1]	X	Spinal cord (3 levels)
X	Stomach[1]	X	Lymph nodes[1]	X	Pituitary
X	Duodenum[1]	X	Spleen	X	Eyes (optic nerve)[1]
X	Jejunum[1]	X	Thymus		
X	Ileum[1]				
X	Cecum[1]				
X	Colon[1]				
X	Rectum		Urogenital		Glandular
XX	Liver[1]	XX	Kidneys[1]	XX	Adrenals
X	Gallbladder[1]	X	Urinary bladder[1]		Lacrimal gland
X	Pancreas[1]	XX	Testes[1]	X	Mammary gland[1]
		X	Epididymides	X	Thyroids
		X	Prostate	X	Parathyrcids[1]
		X	Seminal vesicle		Harderian glands
	Respiratory	X	Ovaries		
X	Trachea[1]	X	Uterus		
X	Lung[1]				
					Other
				X	Bone (sternum and femur)
				X	Skeletal muscle
				X	Skin
				X	All gross lesions and masses

All tissues of control and high-dose groups were examined for animals sacrificed by design, and for the few that died or were sacrificed moribund. For all animals of the main study receiving 1000 ppm or 4000 ppm, only the lungs, liver, gallbladder and kidneys were evaluated histopathologically. No histopathology was performed on the animals in the supplementary study.

[1]Recommended by Subdivision F (November 1984) Guidelines.

Results:

a. Organ Weights: A statistically significant ($p < 0.05$ for males; $p < 0.01$ for females) decrease in absolute liver weights was noted in males (14.8%) and females (11.6%) receiving 8000 ppm for 78 weeks; absolute brain weight was significantly ($p < 0.05$) decreased in males (1.4%) receiving 8000 ppm for 78 weeks. Absolute kidney weights were significantly decreased ($p < 0.01$) in males receiving 1000, 4000, and 8000 ppm, and in females receiving 4000 and 8000 ppm for 78 weeks. The absolute kidney weights were reduced by 16.1% and 7.2% in males and females receiving 8000 ppm, respectively. The organ weight reductions were attributed by the study author to a concurrent decrease in body weight in these animals. However, the study author did not provide data on organ-to-body weight ratios to support this conclusion. On the basis of the reviewers' calculations (results presented in Table 3), a dose-related decrease in kidney-to-body weight ratio was seen in males receiving 1000, 4000, and 8000 ppm. A significant ($p < 0.01$) increase in kidney-to-body weight was seen in all dosed female groups. Although the decrease reached statistical significance ($p < 0.01$) in high-dose males, the decrease was marginal (8%). In addition, a statistically significant ($p < 0.01$) and dose-related increase in brain-to-body weight ratio was noted in males and females. Brain-to-body weight ratios were increased by 16.3% and 18.7% in high-dose males and females, respectively. There was no significant effect of quinclorac on liver-to-body weight ratios in either males or females. The toxicological significance of these organ weight changes is not clear, since there was a lack of corresponding histological changes in these organs. A statistically significant ($p < 0.01$) decrease in absolute liver weights was also noted in males receiving 4000 or 8000 ppm for 6 months; absolute kidney weight was significantly ($p < 0.01$) decreased in males receiving 1000, 4000, or 8000 ppm for 6 months. Likewise, the organ weight reductions in males were not regarded by the study author to be treatment-related because of a concurrent decrease of mean body weight in these males. Once more, data on relative organ weights were not provided by the study author. In the supplementary study, the administration of 250 ppm to mice for 6 months did not cause any compound-related weight changes. Although administration of this same dose to mice for 78 weeks led to a statistically significant ($p < 0.05$) decrease in the relative kidney and adrenal weights in females, these weight changes were regarded by the study author to be incidental. As mentioned above, the reviewers' calculations

TABLE 3. Selected Organ Weights (Mean ± S.D.) and Organ-to-Body Weight Ratios in Mice Fed Quinclorac for 78 Weeks[a]

Dietary Level (ppm)	Kidney		Brain		Liver	
	Absolute (g)	Relative to Body (g)	Absolute (g)	Relative to Body (g)	Absolute (g)	Relative to Body (g)
			Males			
0	0.5900 ± 0.0690	0.0174 ± 0.0016[b]	0.4950 ± 0.0130	0.0147 ± 0.0016[b]	1.258 ± 0.382	0.0371 ± 0.0110
1000	0.5420 ± 0.0450**	0.0175 ± 0.0020	0.4890 ± 0.0160	0.0158 ± 0.0018**	1.141 ± 0.192	0.0369 ± 0.0069
4000	0.4920 ± 0.0380**	0.0168 ± 0.0018	0.4890 ± 0.0160	0.0167 ± 0.0014**	1.175 ± 0.545	0.0400 ± 0.0182
8000	0.4550 ± 0.0410**	0.0160 ± 0.0016**	0.4830 ± 0.0140*	0.0171 ± 0.0012**	1.072 ± 0.097*	0.0376 ± 0.0039
			Females			
0	0.4040 ± 0.0330	0.0122 ± 0.0016	0.5080 ± 0.0140	0.0155 ± 0.0024**	1.229 ± 0.1600	0.0369 ± 0.0045
1000	0.3950 ± 0.0440	0.0139 ± 0.0027**	0.5010 ± 0.0170	0.0177 ± 0.0026**	1.116 ± 0.1300	0.0398 ± 0.0083
4000	0.3840 ± 0.0280**	0.0136 ± 0.0018**	0.5040 ± 0.0130	0.0178 ± 0.0020**	1.138 ± 0.4540	0.0401 ± 0.0155
8000	0.3750 ± 0.0300**	0.0136 ± 0.0020**	0.5080 ± 0.0300	0.0184 ± 0.0020**	1.087 ± 0.0980**	0.0394 ± 0.0056

[a]Organ-to-Body Weights Ratios were calculated by the reviewers. Significance of pairwise comparison denoted at dose groups by ANOVA.

[b]Significant dose-related trend denoted at controls by linear regression; analysis performed by the reviewers.

*Significantly different from control values ($p < 0.05$).

**Significantly different from control values ($p < 0.01$).

revealed that there was a statistically significant ($p < 0.01$) and dose-related decrease in relative kidney weights in males, and a significant increase in relative kidney weights in females in the main study

b. Gross Pathology: No gross pathological lesions attributable to administration of quinclorac were found in any tissue of any mouse.

c. Microscopic Pathology:

1) Nonneoplastic: No histopathological lesions attributable to administration of quinclorac were found in any tissue of any mouse. However, a number of incidental and spontaneous tissue alterations were seen in mice treated orally with 1000, 4000, or 8000 ppm quinclorac for 6 months or 78 weeks. Table 4 summarizes representative nonneoplastic findings in rats fed quinclorac for 78 weeks. In males, a negative trend was noted in centrilobular fatty infiltration in the liver, pancreatic infiltration, and sublingual gland/lymphoid cell infiltration; in females, a negative trend was noted in focal liver cell necrosis, diffuse fatty liver cell infiltration, infiltration of mandibular glands, and pancreatic infiltration. A positive trend was noted in horny cyst of the bulbo-urethral gland, and in focal necrosis in the liver in males. Tissue alterations seen in male and female mice treated with quinclorac for 6 months included a decrease in focal lymphoid infiltration in the kidneys of females receiving 8000 ppm, a decrease in lymphoid infiltration in the prostate of high-dose males, and a decrease in infiltration in the sublingual glands of high-dose females. A negative trend was noted in focal infiltration in the kidneys of males and females, in infiltration in the prostate of males, and in infiltration of the sublingual glands in females.

2) Neoplastic: No neoplastic lesions attributable to administration of any dose of quinclorac for 6 months or 78 weeks were found in any tissue of any mouse. A negative trend was noted in hepatocellular carcinoma in males treated with quinclorac for 78 weeks. The incidence of hepatocellular

TABLE 4. Representative Nonneoplastic Findings in Mice Fed Quinclorac for 78 Weeks

Organ/Finding	Dietary Level (ppm)							
	Males				Females			
	0	1000	4000	8000	0	1000	4000	8000
Sublingual Glands	(50)[a]	(1)	(1)	(50)	(50)	(1)	(1)	(50)
Lymphoid cell infiltration	43	1	0	33	45	1	0	44
Mandibular Glands	(48)	(0)	(1)	(49)	(50)	(1)	(1)	(50)
Lymphoid cell infiltration	2	0	0	0	8	0	0	2
Liver	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Lymphoid cell infiltration	16	14	11	17	34	32	24	31
Necrosis, focal	1	0	1	4	3	2	1	0
Fatty infiltration, centrilobular	4	2	2	0	0	2	5	5
Fatty infiltration, diffuse	45	45	41	47	44	32	33	29
Pancreas	(50)	(2)	(1)	(50)	(50)	(1)	(1)	(50)
Infiltration	1	0	0	4	31	0	0	19
Kidneys	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Infiltration, focal	32	22	21	22	38	35	30	37
Bulbo-urethral Gland	(32)	(2)	(2)	(1)	(0)	(0)	(0)	(0)
Horny cyst	2	1	2	1	0	0	0	0
Uterus					(50)	(1)	(1)	(50)
Endometriosis	0	0	0	0	45	1	5	38
Dilatation	0	0	0	0	7	3	3	5

[a]The numbers in parentheses indicate the number of animals with specific tissue examined histologically.

carcinoma was 3/50 (control males), 2/50 (low-dose males), 1/50 (mid-dose males), and 0/50 (high-dose males). One control male had a hepatocellular adenoma; no liver tumors were observed in females. The incidence of malignant lymphomas was 4/50 (control females), 1/50 (low-dose females), 4/50 (mid-dose females), 2/50 (high-dose females), 1/50 (control males), and 0/50 (low-, mid- and high-dose males). In the main groups (50 animals/sex/group), the number of animals with tumors was 8, 5, 5, and 2 males and 9, 1, 4, and 7 females at dose levels of 0, 1000, 4000, and 8000 ppm, respectively. At these dose levels, the number of animals with malignant tumors was 5, 3, 3, and 0 males and 7, 1, 4, and 4 females, respectively.

D. STUDY AUTHORS' CONCLUSIONS:

Quinclorac was administered to mice in doses of 250, 1000, 4000, or 8000 ppm via the diet over a period of 6 months or 78 weeks. Dietary administration of quinclorac to mice at dose levels of 1000, 4000, and 8000 ppm for 78 weeks led to a statistically significant reduced body weight in males and females. Treatment-related reductions in body weights were seen in males receiving 1000, 4000, or 8000 ppm and in females receiving 8000 ppm after 6 months of compound administration. Administration of 8000 ppm for 78 weeks caused a decrease in the absolute liver weights and absolute brain weights of males, and a decrease in the absolute liver weights of females. The kidney weights were found to be decreased in males receiving 1000, 4000, or 8000 ppm and in the females receiving 4000 or 8000 ppm for 78 weeks. In mice receiving quinclorac for 6 months, a decrease in the absolute liver weights of mid-dose and high-dose males, and a decrease in the absolute kidney weights of all treated males were noted. The reduced organ weights in male and female mice seen after administration of quinclorac for 6 months or 78 weeks were not considered to be substance-related because of concurrent decreases in the body weights of these mice. There was an absence of morphological correlates in these organs. The administration of 1000, 4000, or 8000 ppm quinclorac over a period of 78 weeks to male and female mice did not cause any hematological changes attributable to the substance administered. However, a marginal decrease in the hematocrit values was noted in both sexes receiving 8000 ppm for 6 months. All gross and histopathological changes seen in mice following administration of quinclorac for 6 months or 78 weeks were considered to be spontaneous, rather than compound-induced. Dietary administration of quinclorac to mice for 6 months or 78 weeks led to no signs of toxicity. During the course of the study, no

carcinogenic potential of the test substance could be detected in male and female mice. The no-effect level is 250 ppm.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

The main study design was complete and adequate. In general, the data were adequately organized and reported. Dose levels were appropriately selected on the basis of previous toxicity studies. Summary data were supported by individual animal data, and mean values that were validated agreed with the author's values.

Administration of quinclorac to mice affected only body weight and organ weight. At the end of 13 weeks, body weights in males and females receiving 8000 ppm were significantly lower than controls by 9.6% and 7.4%, respectively. At termination, mean body weights in males receiving 1000, 4000, or 8000 ppm for 78 weeks were 7.9%, 13.5%, and 15.9% lower ($p < 0.01$) than controls, respectively; in females receiving the same doses, the body weights were 14.3%, 15.2%, and 17.9% lower than controls. Treatment-related body weight reductions compared with controls were also noted in males and females receiving 4000 or 8000 ppm for 6 months. Mean body weights were significantly ($p < 0.01$) lower than the controls in males receiving 8000 ppm (7.7 to 16.1% lower) between months 1.4 and 6.0, while mean body weights were 4.4 to 8.8% lower ($p < 0.01$) in females receiving this dose between months 0.47 and 2.8. Mean body weights were also significantly ($p < 0.01$) lower than controls in males receiving 4000 ppm (8.6 to 14.5% lower) between months 2.1 and 6.0. Significant reductions in the body weights (up to 9%) occurred sporadically in low-dose males treated orally with quinclorac for 6 months. Female mice receiving 1000 and 4000 ppm for 6 months showed no differences in body weight when compared with controls. Male and female mice receiving 250 ppm for either 6 months or 78 weeks did not exhibit any significant differences in body weights when compared with controls. Organ weight reductions were noted in males and females receiving quinclorac for 6 months or 78 weeks. The absolute liver weights were reduced by 14.8% and 11.6% in males and females, respectively receiving 8000 ppm for 78 weeks, while absolute kidney weights were reduced by 16.1% and 7.2% in males and females, respectively. Organ weight reductions also occurred in mice following administration of quinclorac for 6 months. In contrast to the main study, a decrease in the absolute liver weights was seen in mid- and high-dose males only. Also, a decrease in the absolute kidney weights was noted in all treated males. The reduced organ weights in male and female mice receiving quinclorac for 6 months or 78 weeks were not regarded by the study author to be substance-related owing to concurrent decreases in the body weights of these animals. However, the study author did not provide data on organ-to-body

weight ratios to support this conclusion. On the basis of the reviewers' calculations, a dose-related decrease in relative kidney weights was seen in males receiving 1000, 4000, and 8000 ppm for 78 weeks. An increase in relative kidney weights was seen in females at these doses. The decrease was marginal (8%) but significant in the high-dose males. Also, a statistically significant and dose-related increase in relative brain weights was seen in the high-dose males and females. There was no correlation between organ weight changes and histopathological changes.

A slight decrease in hematocrit values was noted in males (4.7% decrease) and females (40% decrease) receiving 8000 ppm for 6 months. The study author considered the decrease in hematocrit values to be incidental, since this finding was not present in the main study (78 weeks). Non-treatment-related effects on other hematological parameters were not of biological significance.

There was no effect of dosing on mortality, gross pathology, histopathology, food consumption, or clinical signs. We agree with the study author that under the conditions of the study, quinclorac was not oncogenic.

We agree with the study author's assessment of a NOEL of 250 ppm for systemic toxicity. Based on the effects on body weights, the LOEL is 1000 ppm. On the basis of body weight data, we concluded that a maximum tolerated dose (MTD) was approached in males and females at 8000 ppm.

EPA No.: 68D80056
DYNAMAC No.: 247-L
TASK No.: 2-47L
February 13, 1990

DATA EVALUATION RECORD

QUINCLORAC

Developmental Toxicity Study in Rabbits

STUDY IDENTIFICATION: Hellwig, J. Report on the study of the prenatal toxicity of Registration Number 150 732 in rabbits after oral administration (gavage). (Unpublished study No. 88/0099 conducted by BASF Aktiengesellschaft, Federal Republic of Germany, and submitted by BASF Corporation Chemicals Division, Parsippany, NJ; dated April 5, 1988.) MRID No. 410635-25.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: William L. McLellan for

Date: Feb. 13, 1990

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1. CHEMICAL: 3,7-Dichloro-8-quinolinecarboxylic acid.

2. TEST MATERIAL: Reg. No. 150 732, batch No. N 57 III/2, 96.5% pure, crystalline.

3. STUDY/ACTION TYPE: Developmental toxicity study in rabbits.

4. STUDY IDENTIFICATION: Hellwig, J. Report on the study of the prenatal toxicity of Registration Number 150 732 in rabbits after oral administration (gavage). (Unpublished study No. 88/0099 conducted by BASF Aktiengesellschaft, Federal Republic of Germany, and submitted by BASF Corporation Chemicals Division, Parsippany, NJ; dated April 5, 1988.) MRID No. 410635-25.

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(H-7509C)

Signature: Marion Copley
Date: 3/29/90

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DATA EVALUATION RECORD

STUDY TYPE: Developmental toxicity. Guideline §83-3.

MRID NUMBER: 410635-25.

TEST MATERIAL: 3,7-Dichloro-8-quinolinecarboxylic acid.

SYNONYM(S): Reg. No. 150 732, Quinclorac, Facet, BAS 514 ..H.

STUDY NUMBER: 88/0099.

SPONSOR: BASF Corporation Chemicals Division, Parsippany, NJ.

TESTING FACILITY: BASF Aktiengesellschaft, Federal Republic of Germany.

TITLE OF REPORT: Report on the study of the prenatal toxicity of Registration Number 150 732 in rabbits after oral administration (gavage).

AUTHOR: Hellwig, J.

REPORT ISSUED: April 5, 1988.

CONCLUSIONS: A developmental toxicity study was conducted in which Himalayan rabbits were administered quinclorac via gavage at 0, 70, 200, and 600 mg/kg/day during gestational days (GD) 7 through 19. Maternal toxicity, observed at the highest dose level, was manifested as reduced food consumption and weight gain during treatment, increased water consumption during the gestational period, increased mortality rate, and discoloration of the kidney. At the mid-dose level, nonsignificant reductions in weight gain and food consumption during the treatment period, and corrected weight gain, were observed. However, owing to the lack of supporting data (regarding analysis of doses and selected individual animal observations), the maternal NOEL and LOEL cannot be determined.

Developmental toxicity, also observed at the highest dose level, was manifested as an increased rate of resorptions and postimplantation loss, a decrease in the number of live fetuses, and reduced fetal body weight. However, owing to the lack of supporting data (regarding analysis of doses and selected individual animal observations), the developmental NOEL and LOEL cannot be determined.

Classification: CORE Supplementary Data. This study may be upgraded to CORE Minimum Data if the above-discussed supporting data are submitted so that the results can be verified.

A. MATERIALS:

Test Compound: Purity: 98.3%.
Description: Crystalline.
Lot No.: Not reported, batch No. N 57 III 2.
Contaminants: Not reported.

Vehicle(s): 0.5% Carboxymethyl cellulose in double distilled water.

Test Animals: Species: Rabbit.
Strain: Himalayan (Chbb: HM).
Source: Dr. Karl Thomae, Biberach an der Riss, Federal Republic of Germany.
Age: 23-30 weeks on GD 0.
Weight: 2007-2509 g on GD 0.

B. STUDY DESIGN:

This study was designed to assess the potential of quinclorac to cause developmental toxicity in rabbits when administered daily via gavage from GD 7 through 19, inclusive.

Mating: Does were fertilized by means of artificial insemination. The day of insemination was designated as GD 0.

Group Arrangement: Inseminated females were randomly assigned to dose groups based on body weight during the acclimation period as follows:

Test Group	Dose Level (mg/kg/day)	Number Assigned
Control	0	15
Low dose	70	15
Mid dose	200	15
High dose	600	15

Dosing: Doses were administered daily on GD 7 through 19 in a volume of 10 mL/kg, based on body weights determined on GD 7. Dosing suspensions were prepared daily prior to administration and analyzed for stability and concentration. Homogeneity, stability, and concentration were also analyzed prior to the start of the study. Selection of doses was based on a preliminary study in rabbits (three/group) in which doses of 0, 100, 400, and 600 mg/kg/day were administered via gavage from GD 6 to 18. Reductions in food intake, body weight gain, and placental and fetal weights were observed at 400 and 600 mg/kg/day.

Observations: Animals were observed at least once daily for mortality and overt signs of toxicity. Body weights were recorded on GD 0, 2, 4, 7, 9, 11, 14, 16, 19, 21, 23, 25, 28, and 29. Food and water consumption were recorded daily during the entire study period. Females were sacrificed on GD 29, and litters were delivered by cesarean section. Examination of the dams at sacrifice included the following:

- Gross pathology assessment;
- Number of corpora lutea;
- Gravid uterine weight;
- Placental weight;
- Number of implantation sites; and
- Number of resorptions and live and dead fetuses.

The viable fetuses were examined in the following manner:

- Individual fetuses were X-rayed, weighed, and sexed;

- External abnormalities were recorded;

- All fetal heads were processed according to the method of Wilson (1965);

- Visceral alterations were examined in situ and recorded; and

- Skeletal alterations were recorded using a modified method of Dawson (1926).

Statistical Analysis: The following analyses were conducted:

- Body weight, uterine weight, and placental weight--William's test;

- Conception rate, mortality rate, and all fetal findings--Fisher's Exact test; and

- Numbers of corpora lutea and implantation sites and percent live and dead fetuses per pregnant animal--Krauth test.

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated February 21, 1989, was provided.

- A signed Statement of Compliance with EPA GLP's was not provided. This study was conducted in accordance with the Organization of Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice.

- A signed Quality Assurance Statement, dated April 5, 1988, was provided.

C. RESULTS:

The following results have been reported by the study author.

1. Dose Analysis: Analyses for concentration showed a range of 92-110% within target concentration. Homogeneity and stability of dosing solutions were demonstrated for a period of at least 2 days.

2. Maternal Toxicity:

Mortality: A total of six animals were lost from the high-dose group. Two animals died during GD 14 and 20; death was preceded by poor general health that included reduced/no defecation and apathy. One animal died on GD 16 from a gavage error. A further two animals were sacrificed on GD 18 and 21 after showing signs of abortion and one animal was sacrificed on GD 21 because of poor health.

Abortion: Abortions occurred in two high-dose animals.

Clinical Observations: A summary of clinical observations is presented in Table 1. Several compound-related clinical symptoms were observed during and after treatment among high-dose animals. These included reduced/no defecation, diarrhea, apathy, and/or poor general state.

Body Weight: A summary of maternal body weight gain and corrected weight gain is presented in Table 2. Body weight gain was significantly ($p < 0.01$) reduced in the high-dose group and significantly increased ($p < 0.05$) after treatment. In the mid-dose group, body weight gain was reduced during the treatment period, although it was never significantly different from the control group. Corrected weight gain was slightly reduced in the mid-dose group and significantly ($p < 0.01$) reduced in the high-dose group. Gravid uterine weight among high-dose animals was significantly reduced by 21% ($p < 0.05$; data not shown).

Food and Water Consumption: Summaries of food and water consumption data are presented in Tables 3 and 4, respectively. In the mid- and high-dose groups, food consumption was decreased during treatment (13 and 47%, respectively). Water consumption among treated animals did not differ markedly from that observed in the controls. No statistical evaluation of these parameters was reported.

Gross Pathological Observations: A summary of maternal necropsy observations is presented in Table 5. Among high-dose animals, a variety of findings were observed that included: heart dilation, watery feces in the large intestine, no feces in the small intestine, hypoplasia and discoloration of the cortex in the kidney, discoloration of the liver, blood in the bladder, thickened content and ulceration in the stomach, and incarcerated placenta. All dose groups exhibited amber-colored liquid in the abdomen and cysts in the uterine mucosa. One control doe had a blind-ending uterine horn, and one mid-dose doe had an increased amount of amniotic fluid.

TABLE 1. Summary of Clinical Observations[a]

Finding	Dose Level (mg/kg/day) 0	70	200	600
No. animals examined	15	15	15	15
Vaginal hemorrhage	0[b]	0	1	0
Poor general state	0	0	0	5
Apathy	0	0	0	2
Blood in bedding	1	0	0	2
Signs of anemia	0	0	0	1
Edema in anal and/or genital region	1	0	0	0
Reduced defecation	0	1	1	14
No defecation	0	0	0	4
Diarrhea	0	0	0	5

[a]Data were extracted from study No. 88/0099, Tables 20 and 21.

[b]Represents the total number of animals exhibiting the clinical sign at least once during the study.

TABLE 2. Body Weight Gains (g ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-7)	Dosing Period (GD 7-19)	Post-dosing Period (GD 19-29)	Entire Gestation Period (GD 0-29)	Corrected Weight Gain[b]
0	92 ± 50	77 ± 86	171 ± 80	339 ± 156	37 ± 101
70	93 ± 53	79 ± 97	163 ± 85	335 ± 145	42 ± 142
200	90 ± 59	49 ± 65	163 ± 54	303 ± 124	-8 ± 112
600	119 ± 45	-314 ± 295**	250 ± 120*	193 ± 257*	-45 ± 108*

[a]Data were extracted from study No. 88/0099, Tables 16 and 17.

[b]Calculated as total body weight gain minus gravid uterine weight.

*Significantly different from controls ($p < 0.05$).

**Significantly different from controls ($p < 0.01$).

Cesarean Section Observations: A summary of cesarean section data is presented in Table 6. In the high-dose group, although not statistically significant, the number of resorptions increased above controls, while the number of live fetuses decreased. As a result, the postimplantation loss also increased (nonsignificantly) at the high-dose level. In addition, fetal body weight was significantly ($p < 0.05$) reduced in this group.

3. Developmental Toxicity:

A summary of fetal malformations and variations is presented in Table 7.

External Examination: No malformations were observed in any dose group. Pseudoankylosis (variation) was present in all dose groups.

Visceral Examinations: The following malformations were observed: septal defect (one fetus each in the control, low-, and mid-dose groups), agenesia of the gallbladder (two fetuses from one litter in the low-dose group), and herniated diaphragm (one fetus in the high-dose group). The following variations were observed: separated origin of carotids (present in all groups) and hypoplasia of the gallbladder (one fetus, mid-dose group).

Skeletal Examination: Fused ribs (malformation) were observed in one fetus in the high-dose group. Variations in the sternebrae (fused/irregularly shaped/accessory) were present in all groups. The total number of fetuses with skeletal variations was significantly ($p < 0.05$) increased above controls in the high-dose group.

TABLE 3. Summary of Group Total Food Consumption Per Day (g ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-7)	Dosing Period (GD 7-19)	Post-dosing Period (GD 19-29)	Entire Gestation Period (GD 0-29)
0	138 ± 17	108 ± 22	119 ± 18	119 ± 16
70	137 ± 17	105 ± 32	119 ± 18	118 ± 21
200	133 ± 20	94 ± 30	110 ± 21	109 ± 22
600	139 ± 15	51 ± 46	119 ± 18	104 ± 25

[a]Data were extracted from study No. 88/0099, Table 5.

TABLE 4. Summary of Group Total Water Consumption Per Day (g ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-7)	Dosing Period (GD 7-19)	Post-dosing Period (GD 19-29)	Entire Gestation Period (GD 0-29)
0	220 ± 32	168 ± 39	227 ± 52	201 ± 38
70	219 ± 42	187 ± 50	222 ± 52	207 ± 44
200	221 ± 40	195 ± 51	233 ± 51	215 ± 41
600	226 ± 39	170 ± 71	231 ± 80	216 ± 58

[a]Data were extracted from study No. 88/0099, Table 9.

TABLE 5. Summary of Maternal Necropsy Observations[a]

Finding[b]	Dose Level (mg/kg/day) 0	70	200	600
No. animals examined	15	15	15	15
Heart:				
dilation	0	0	0	1
Abdominal cavity:				
amber-colored liquid	8	10	10	2
Stomach:				
thickened content	0	0	0	1
ulceration	0	0	0	1
Liver:				
light brown-gray	0	0	0	1
Kidney:				
hypoplasia	0	0	0	1
light cortex	0	0	0	5
Large intestine:				
watery feces	0	0	0	5
Small intestine:				
no feces	0	0	0	2
Bladder:				
bloody contents	0	0	1	1
blind-ending uterine horn	1	0	0	0
Uterus:				
cyst in mucosa	1	2	3	1
increased amniotic fluid	0	0	1	0
incarcerated placenta	0	0	0	2

[a]Data were extracted from study No. 88/0099, Tables 22 and 23.

[b]More than one finding may be observed in one animal.

TABLE 6. Cesarean Section Observations[a]

Parameter	Dose Level (mg/kg/day) 0	70	200	600
No. animals assigned	15	15	15	15
No. animals pregnant	14	13	13	14
Pregnancy rate (%)	93	87	87	93
Maternal wastage				
No. died/pregnant	0	0	0	3[b]
No. sacrificed moribund/ pregnant	0	0	0	1
No. aborted	0	0	0	2
No. animals evaluated	14	13	13	8
Total corpora lutea	107	90	91	56
Corpora lutea/dam	7.6	6.9	7.0	7.0
Total implantations	82	78	78	50
Implantations/dam	5.9	6.0	6.0	6.3
Total live fetuses	75	69	75	35
Live fetuses/dam	5.4	5.3	5.8	4.4
Total resorptions	7	9	3	15
Early	2	3	1	15
Intermediate	3	5	2	0
Late	2	1	0	0
Resorptions/dam	0.5	0.7	0.2	1.9
Total dead fetuses	0	0	0	0
Dead fetuses/dam	0	0	0	0
Fetal weight/litter (g)	42.5	40.9	39.9	39.2*
Preimplantation loss (%)	22.6	15.7	15.1	12.1
Postimplantation loss (%)	12.2	9.6	3.3	26.3
Sex ratio[c]	44	57	36	37

[a]Data were extracted from study No. 88/0099, Tables 1, 24, and 25.

[b]Includes one animal that died as a result of a gavage error.

[c]Calculated by reviewers as No. males per group/Total No. pups per group. The data were analyzed using Fisher's Exact test.

*Significantly different from controls ($p < 0.05$).

TABLE 7. Summary of Fetal Malformations and Variations[a]

Finding[b]	Dose Level (mg/kg/day) 0	70	200	600
No. fetuses (litters) examined	75 (13)	69 (13)	75 (13)	35 (6)[c]
External examination				
Malformation:				
None				
Variation:				
Pseudoankylosis	1 (1)	1 (1)	1 (1)	2 (1)
Total No. fetuses (litters)				
with malformations	0	0	0	0
with variations	1 (1)	1 (1)	1 (1)	2 (1)
Visceral examination				
Malformation:				
Septal defect	1 (1)	1 (1)	1 (1)	0
Hernia diaphragmatica	0	0	0	1 (1)
Agenesis of gallbladder	0	2 (1)	0	0
Variation:				
Hypoplasia of gallbladder	0	1 (1)	0	0
Separated origin of carotids	38 (11)	42 (12)	43 (12)	17 (5)
Total No. fetuses (litters)				
with malformations	1 (1)	3 (2)	1 (1)	1 (1)
with variations	38 (11)	43 (12)	43 (12)	17 (5)
Skeletal examination				
Malformation:				
Fused ribs	0	0	0	1 (1)
Variation:				
Shortened ribs	0	0	0	2 (1)
Accessory ribs	0	1 (1)	0	0
Fused sternebrae	4 (3)	8 (5)	4 (3)	3 (2)
Irregularly shaped sternebrae	4 (3)	5 (3)	4 (4)	3 (3)
Accessory sternebrae	1 (1)	2 (2)	0	3 (3)
Retardation:				
Cervical vert. body/bodies, only one ossification center	1 (1)	0	0	1 (1)
Thoracic vertebral body/bodies, dumbbell-shaped	0	0	0	1 (1)
Sternebrae not ossified	26 (10)	17 (9)	20 (7)	16 (5)
Sternebrae incompletely ossified or reduced in size	15 (11)	14 (10)	7 (6)	7 (5)
Talus incompletely ossified	1 (1)	0	0	0
Total No. fetuses (litters)				
with malformations	0	0	0	1 (1)
with variations	9 (6)	13 (8)	7 (5)	11* (6*)
with retardations	41 (12)	31 (12)	27* (8)	23 (6)

[a]Data were extracted from study No. 88/0099, Tables 27-38.

[b]More than one type of anomaly may be found in one fetus.

[c]Two dams had no live fetuses.

*Significantly different from controls ($p < 0.05$).

Skeletal retardations consisted of incomplete/absent ossification in the sternebrae, vertebrae, and talus and were observed in all groups.

D. DISCUSSION/CONCLUSION:

1. Dose Analysis: The results of the stability and homogeneity tests were reported in qualitative terms. However, no data were submitted to verify the results.

2. Maternal Toxicity: Maternal toxicity (evidenced by clinical signs of toxicity, increased mortality rate, decreased food consumption during treatment, and decreased weight gain during treatment) was observed in does receiving 600 mg quinclorac/kg/day. The nonsignificant reductions in weight gain and food consumption observed in does receiving 200 mg/kg/day are considered biologically important since these effects were dose-dependent. The analysis of dosing solutions and selected individual animal observations (for corpora lutea and food and water consumption) could not be verified owing to a lack of supporting data. Consequently, the maternal NOEL and LOEL were not determined.

3. Developmental Toxicity:

   a. Deaths/Resorptions: There are clear signs of developmental toxicity. Because of the high rate of maternal toxicity (due to death or abortion) and complete resorption in 2 does in the high-dose group, only 6 of 15 litters were evaluated. This low number may not be a representative sample for the high-dose group. Among the six animals that died or were sacrificed, all were pregnant, and in all the does, the dead implantations reported were smaller than expected at the GD of death (see CBI, Tables 42 and 43, and page 23). Had these animals been included in the statistical evaluation, the number of resorptions might have been statistically significant. Thus, the reviewers are convinced that these effects are compound-related and biologically important.

   b. Altered Growth: A significant ($p < 0.05$) decrease in fetal body weight was observed in the high-dose group.

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c. Developmental Anomalies: The number of litters with any kind of malformation(s) was never significantly different from controls among the treated groups. The total number of fetuses with skeletal variations, however, increased above controls in the high-dose groups.

Based on these results, it was concluded that developmental toxicity was present at the highest dose level. Although few litters were evaluated at this dose level, the reviewers believe that the observations can be useful. The lack of supporting data (for analysis of dosing solutions and individual fetal sex determination) makes it impossible to verify the results and thus prevents a determination of the developmental NOEL and LOEL.

4. Study Deficiencies:

a. Data to support the results of stability and homogeneity of dosing solutions were not provided.

b. Too few animals were evaluated in the high-dose group.

c. Individual animal data for food and water consumption, number of corpora lutea, and fetal sex were not submitted.

d. The study was not conducted according to EPA GLPs. It was, however, conducted according to OECD GLPs.

E. CLASSIFICATION: CORE Supplementary Data.

Maternal NOEL = Not determined.
Maternal LOEL = Not determined.
Developmental Toxicity NOEL = Not determined.
Developmental Toxicity LOEL = Not determined.

F. RISK ASSESSMENT: Not applicable.

EPA No.: 68D80056
DYNAMAC No.: 247-K
TASK No.: 2-47K
February 13, 1990

DATA EVALUATION RECORD

QUINCLORAC

Developmental Toxicity Study in Rats

STUDY IDENTIFICATION: Hellwig, J. Report on the study to determine the prenatal toxicity of Registration Number 150 732 in rats after oral administration (gavage). (Unpublished study No. 87/0167 conducted by BASF Aktiengesellschaft, Federal Republic of Germany, and submitted by BASF Corporation Chemicals Division, Parsippany, NJ; dated May 12, 1987.) MRID No. 410635-24.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: William L. Weir
Date: Feb. 13, 1990

This study has been upgraded to Core-Minimum (see Document #).

1. CHEMICAL: 3,7-dichloro-8-quinolinecarboxylic acid.

2. TEST MATERIAL: Reg. No. 150 732, batch No. N 32, 96.5% pure.

3. STUDY/ACTION TYPE: Developmental toxicity study in rats.

4. STUDY IDENTIFICATION: Hellwig, J. Report on the study to determine the prenatal toxicity of Registration Number 150 732 in rats after oral administration (gavage). (Unpublished study No. 87/0167 conducted by BASF Aktiengesellschaft, Federal Republic of Germany, and submitted by BASF Corporation Chemicals Division, Parsippany, NJ; dated May 12, 1987.) MRID No. 410635-24.

5. REVIEWED BY:

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Principal Reviewer
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Date: February 13, 1990

Patricia Turck, M.S.
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Dynamac Corporation

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Date: February 13, 1990

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Signature: Marion Copley
Date: 3/21/90

TABLE 8. Incidence of Nonneoplastic Lesions in Dogs Fed Reg. No. 150 732[a]

Dietary Level (ppm)	Dietary Level (ppm)							
	Males				Females			
	0	1,000	4,000	12,000	0	1,000	4,000	12,000
Liver								
Congestion	0	0	0	1	0	0	0	0
Single cell necrosis	0	0	0	2	0	0	0	2
Pancreas								
Congestion	0	0	0	1	0	0	0	0
Lung								
Congestion	0	0	0	1	0	0	0	0
Kidneys								
Degeneration: hydropic	0	0	0	2	0	0	0	2
Fatty infiltration	6	5	4	6	6	6	6	6
Calcium deposition	6	6	5	6	6	6	6	5
Congestion	0	0	0	1	0	0	0	0
Prostate								
Hypoplasia	0	0	2	1				
Thymus								
Cyst(s), epithelial	0	1	2	1	4	2	3	3
Mesenteric Lymph Node								
Congestion	0	0	0	1	0	0	0	0

[a]Data were extracted from study No. 88/0029, pages 235 and 236, based on six dogs/sex/group.

D. STUDY AUTHOR'S CONCLUSIONS:

Quinclorac (Reg. No. 150 732) was administered to groups of six dogs/sex in their diet for 12 months at doses of 1,000, 4,000, and 12,000 ppm. A group of six dogs per sex were untreated and served as a control. There was one death during the study, which was not attributed to the administration of the test substance. At the 12,000-ppm dose level, there was a treatment-related adverse effect on body weight change and food efficiency in both sexes. There were decreases in hemoglobin, erythrocyte count, hematocrit, mean hemoglobin content per erythrocyte (MCH), and a reduction in the mean corpuscular volume (MCV) in both sexes. There were decreases of no clinical significance in creatinine, urea, total protein, albumin, calcium, triglycerides, total bilirubin, alkaline phosphatase, and glutamate pyruvate transaminase in both sexes. Increased absolute and relative liver weights and increased relative kidney weights were observed in both sexes. Microscopic findings consisted of increased mononuclear infiltrates in the liver, and single cell necrosis in two male and two female dogs. Hydropic degeneration of the kidneys occurred in individual animals of both sexes.

At the 4000-ppm dose level, there was a marginal decrease in body weight change and food efficiency in male dogs. Clinical chemistry findings consisted of a decrease in creatinine, urea, and total protein values in both sexes, a drop in the calcium level in females, and a decrease in bilirubin concentration and alkaline phosphatase activity in males. All of these clinical findings are of no biological concern. Relative kidney weights were increased in male dogs. There were no treatment-related changes in the 1000-ppm group.

The author considered the retarded body weight change and the adverse effect on food efficiency to be the cause of the effects on individual clinicochemical parameters, the hypochromic anemia, and the increase in liver weights and relative kidney weights. Histopathology revealed no clear findings correlating to the increased liver weights; hydropic degeneration of the kidney was observed in four dogs in the 12,000-ppm group.

The author concluded, on the basis of the clinochemical findings, the no-observed-effect level (NOEL) is in a range between 1000 and 4000 ppm for both male and female animals.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

The study design was complete and adequate, and the data were well reported. Dose levels were appropriately selected on the basis of a previous 4-week range-finding study. Summary data were supported by individual animal data, and mean values that were validated agreed with the study author's values. However, no data were provided regarding analysis of homogeneity of diets. Only one animal died during the study, and this death

was not treatment related. Mean body weights and body weight gains of all treated groups of animals were reduced throughout the study. Mean body weights were significantly ($p < 0.01$) reduced in 12,000-ppm males; mean body weight gains were similarly affected and significantly reduced in 12,000-ppm dogs of both sexes. This was not related to food consumption, although food efficiency was affected by treatment, especially in the 12,000-ppm group and to a lesser extent in other treated groups. Administration of 12,000 ppm of test substance resulted in significant ($p < 0.01$) reductions in hemoglobin concentration, erythrocyte counts, hematocrit and MCH values, and mean corpuscular volume. Since there was indication of a compensatory reaction of the bone marrow to the reduced number of red blood cells, the study author ruled out hemolytic anemia as a cause of the anemia. The reason for the anemia is unclear. The reduced mean hemoglobin concentrations indicate a disturbed synthesis of heme and hemoglobin as a possible cause of the anemia.

In the 12,000 ppm treatment group, creatinine, urea, total protein, albumin, calcium, triglycerides, total bilirubin, alkaline phosphatase, and glutamate pyruvate transaminase values in both sexes were decreased. Statistically significant decreases were noted for total bilirubin, creatinine, calcium, and albumin. Significant ($p < 0.05$) decreases also were noted only for creatinine values in females at the 1000- and 4000-ppm levels, and males ($p < 0.01$) at the 4000-ppm level, and calcium levels in animals fed 1000 ppm ($p < 0.01$) or 4000 ppm ($p < 0.05$).

Urea decreased in 12,000-ppm males at weeks 26 (nonsignificant) and 52 ($p < 0.05$), and in 4,000-ppm females and 12,000-ppm-females at 52 weeks as compared with controls. The values in 12,000 ppm males, however, were similar to pretest values; in females there was no dose trend at 52 weeks, and the 12,000-ppm female value did not differ from pretest values. Decreases in urea values are not generally indicative of an adverse effect, as are increased values. Total protein decreased in 12,000-ppm females at 13 weeks ($p < 0.01$) and 52 weeks ($p < 0.05$) but were not different from pretest values; the changes were slight, and all were within normal range. Albumin was significantly decreased in 12,000-ppm males at 13, 26, and 52 weeks, and in 12,000-ppm females at 26 and 52 weeks, but there was no trend with time, and the values did not differ from pretest values. Although calcium values were decreased significantly in 12,000-ppm males ($p < .05$ at 12, 26, and 52 weeks) and in females ($p < 0.01$ at 13 and 52 weeks and $p < 0.05$ at 26 weeks), the values are not abnormal and do not differ from pretest values. Triglyceride values showed no pattern related to dose or time, and significant ($p < 0.05$) decreases in 12,000-ppm females at 13 and 26 weeks were not of toxicological importance. Alkaline phosphatase was decreased in 12,000-ppm males and females, but the decreases were significant only at 13 weeks. There were no dose- or time-related trends. Increases rather than decreases in alkaline phosphatase values are toxicologic indications of adverse

DATA EVALUATION RECORD

STUDY TYPE: Developmental toxicity. Guideline §83-3.

MRID NUMBER: 410635-24.

TEST MATERIAL: 3,7-dichloro-8-quinolinecarboxylic acid, reg. No. 150 732, batch No. N 32.

SYNONYM: Quinclorac.

STUDY NUMBER: 87/0167.

SPONSOR: BASF Corporation Chemicals Division, Parsippany, NJ.

TESTING FACILITY: BASF Aktiengesellschaft, Federal Republic of Germany.

TITLE OF REPORT: Report on the study to determine the prenatal toxicity of Registration Number 150 732 in rats after oral administration (gavage).

AUTHOR: Hellwig, J.

REPORT ISSUED: May 12, 1987.

CONCLUSIONS: A developmental toxicity study was conducted in which Wistar rats were administered quinclorac via gavage at 0, 24.4, 146, and 438 mg/kg/day during gestational days 6-15. Maternal toxicity at the highest dose level was manifested as reduced food consumption during treatment, increased water consumption during the gestational period, and an increased mortality rate. No developmental toxicity was observed. Due to lack of supporting data, however (regarding concentration and stability of dosing solutions) NOELs and LOELs cannot be determined.

Classification: CORE Supplementary Data.* This study may be upgraded to CORE Minimum Data if information is provided such that the results of the above-discussed parameters can be verified.

A. MATERIALS:

Test Compound: Purity: 96.5%.
Description: Not reported.
Lot No.: Not reported, batch No. N 32.
Contaminants: Not reported.

Vehicle(s): 0.5% carboxymethylcellulose in distilled water.

Test Animals: Species: Rat.
Strain: Wistar [Chbb: THOM (SPF)].
Source: Dr. K. Thomae GmbH, Biberach, Federal Republic of Germany.
Age: 10-12 weeks at start of study.
Weight: 178-250 g on gestation day 0.

B. STUDY DESIGN: This study was designed to assess the potential of quinclorac to cause developmental toxicity in rats when administered daily via gavage from gestational days (GD) 6 through 15, inclusive.

Mating: One to four females were mated overnight with one fertile male. If sperm were detected in the vaginal smear the following morning, the females were considered fertilized. They were then removed and housed individually. This day was recorded as GD 0.

Group Arrangement: Mated females were randomly assigned to dose groups using a pseudo-random number generator for equally distributed permutations.

* This study has been upgraded to Core-Minimum (see Document #).

Test group	Dose level (mg/kg/day)	Number assigned per group
Control	0	25
Low dose	24.4	25
Mid dose	146.0	25
High dose	438.0	25

Dosing: Doses were administered in a volume of 5 mL/kg based on body weights determined on GD 6. Dosing suspensions were prepared daily prior to administration and analyzed for stability and concentration. Homogeneity of the dose suspensions was not analyzed. Selection of doses was based on two range-finding studies in which doses of 600, 800, and 1000 mg/kg/day were lethal to the dams, but doses of up to 438 mg/kg/day were tolerated.

Observations: Animals were observed daily for mortality and overt signs of toxicity. Body weights and food consumption were recorded on GD 0, 1, 3, 6, 8, 10, 13, 15, 17, and 20. Water consumption was recorded daily during the treatment period and three times per week during the pre- and postdosing periods (specific days were not reported). Females were sacrificed on GD 20, and litters were delivered by cesarean section. Examination of the dams at sacrifice included the following:

- Thoracic and abdominal cavities content;
- Number of corpora lutea;
- Gravid uterine weight;
- Placental weight;
- Fetal uterine position;
- Number of implantation sites; and
- Number of resorptions and live and dead fetuses.

The viable fetuses were examined in the following manner:

- Individual fetuses were weighed, measured (length), and sexed;

- External abnormalities were recorded;

- Visceral abnormalities were recorded for all fetuses using the method of Barrow/Taylor et al. (1969)[1] on approximately 1/3 of the fetuses, and by recording visceral abnormalities on approximately 2/3 of the fetuses prior to their skeletal evaluation; and

- Skeletal abnormalities were recorded using a modified method of Kimmel et al. (1981).[2]

Statistical Analysis: The following analyses were conducted:

- William's test;

- Fisher's Exact test; and

- Krauth's test.

The parameters for which each test was used were not reported.

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated February 20, 1989, was provided.

- A signed Statement of Compliance with EPA GLPs was not provided. This study was conducted in accordance with the Organization of Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice.

- A signed Quality Assurance Statement, dated May 12, 1987, was provided.

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[1]Barrow, M.V., et al. (1969) A rapid method for detecting malformations in rat fetuses. J. Morph. 127:291-306.

[2]Kimmel, C.A. et al. (1981) A rapid procedure for routine double staining of cartilage and bone in fetal and adult animals. Stain Technol. 56:271-273.

C. RESULTS:

The following results were reported by the study author.

1. Dose Analysis: It was reported that analyses for concentration and stability of dosing solutions were within normal limits. However, no data were submitted. Analysis for homogeneity was not performed.

2. Maternal Toxicity:

Mortality: Two high-dose dams died during the study on GDs 11 and 14. One high-dose dam was sacrificed in a moribund condition on GD 13.

Abortion: No abortions were reported.

Clinical Observations: There were no signs of clinical toxicity except for the weight loss experienced by the three dams that died during the study.

Body Weight: A summary of maternal body weight gain is presented in Table 1. Body weight gain at one time point (days 6 to 8) was significantly decreased (7.36 g in controls versus -2.58 g in the high-dose animals) in the high-dose group (data not shown), but it was never different when compared to controls over the entire gestational or dosing period.

Food and Water Consumption: Summaries of food and water consumption data are presented in Tables 2 and 3, respectively. In the high-dose group, food consumption was significantly decreased (10-15%) during treatment days 7-13 (data not shown), while water consumption was significantly increased during the treatment (approximately 54%) and gestational periods (approximately 31%).

Gross Pathological Observations: The two females that died and the one that was sacrificed during the study (all from the high-dose group) had experienced severe weight loss prior to death and displayed severe ulceration in the glandular stomach at necropsy.

Cesarean Section Observations: A summary of cesarean section data is presented in Table 4. No parameter at any dose level was significantly different from controls.

TABLE 1. Mean Body Weight Gains (g ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-6)[b]	Dosing Period (GD 7-15)[b]	Postdosing Period (GD 16-20)[b]	Entire Gestation Period (GD 0-20)
0	26 ± 7.2	50 ± 6.7	69 ± 9.7	145 ± 17.4
24.4	27 ± 6.1	48 ± 7.3	66 ± 14.7	140 ± 23.0
146.0	28 ± 6.3	51 ± 6.7	71 ± 9.8	150 ± 18.3
438.0	27 ± 9.4	44 ± 30.2	68 ± 12.8	140 ± 37.0

[a]Data were extracted from study No. 87/0167, Tables 12 and 13.

[b]Calculated by the reviewers using individual animal data. The statistics used for analysis were ANOVA followed by Dunnett's test.

TABLE 2. Summary of Food Consumption Data (g/animal)[a]

Dose Group mg/kg/day)	Prior to Dosing Period (GD 1-6)[b]	Dosing Period (GD 7-15)[b]	Postdosing Period (GD 16-20)[b]	Entire Gestation Period (GD 1-20)[b]
0	22.5	25.9	29.2	100.3
24.4	21.6	24.8	28.2	96.9
146.0	23.2	26.1	29.3	99.3
438.0	22.7	23.2	28.9	97.2

[a]Data were extracted from study No. 87/0167, Tables 3 and 49.

[b]Calculated by reviewers using mean data. Statistical analysis could not be conducted because individual animal data were not presented.

TABLE 3. Summary of Water Consumption Data[a]

Dose Group (mg/kg/day)	(g/animal/day) Prior to Period (GD 1-6)[b]	Dosing Period (GD 7-15)[b]	Postdosing Period (GD 16-20)[b]	Total g Entire Gestation Period (GD 1-20)
0	24.6	29.0	39.8	607
24.4	23.7	28.3	37.7	586
146.0	25.2	31.7	40.8	641
438.0	24.5	44.6	47.4	782**

[a]Data were extracted from study No. 87,016?, Table 51.

[b]Calculated by reviewers using mean data. Statistics were not conducted because individual animal data were not presented.

**Significantly different from controls ($p < 0.01$)

TABLE 4. Cesarean Section Observations[a]

Parameter	Dose Level (mg/kg/day)			
	0	24.4	146	438
No. animals assigned	25	25	25	25
No. animals pregnant	25	25	23	21
Pregnancy rate (%)	100	100	92	84
Maternal wastage				
No. died/pregnant	0	0	0	2
No. killed/pregnant	0	0	0	1
Total corpora lutea	362	346	343	332
Corpora lutea/dam	14.5	13.8	14.9	15.8
Total implantations	351	336	325	301
Implantations/dam	14.0	13.4	14.1	14.3
Total live fetuses	321	297	307	259
Live fetuses/dam	12.8	11.9	13.4	12.3
Total resorptions	30	39	18	42
Early	23	34	16	38
Intermediate	7	4	2	3
Late	0	1	0	1
Resorptions/dam	1.2	1.6	0.8	2.0
Total dead fetuses	0	0	0	0
Dead fetuses/dam	0	0	0	0
Fetal weight (g)	3.72	3.91**	3.93**	3.98**
Preimplantation loss (%)	3.19	4.29	5.45	7.48
Postimplantation loss (%)	8.23	11.29	5.51	14.12
Sex ratio (% male)[b]	52	47	52	54

[a]Data were extracted from study No. 87/0167, Tables 15 and 21.

[b]Calculated by the reviewers as $\frac{\text{No. males per litter}}{\text{No. viable fetuses per litter}} \times 100$.

Fisher's Exact test was used for statistical analysis.

**Significantly different from controls ($p < 0.01$).

3. Developmental Toxicity

A summary of fetal anomalies is presented in Table 5.

External Examination: In the control group, one fetus had a kinky tail. In the high-dose group, one fetus exhibited anasarca (generalized massive edema).

Visceral Examinations: In the control group, one fetus exhibited situs inversus, and another exhibited microphthalmia. In the low-dose group, one fetus exhibited microphthalmia. In the mid-dose group, one fetus exhibited internal hydrocephalus. In the high-dose group, five fetuses from three litters exhibited anomalies (Table 5). These included microphthalmia, anophthalmia, cleft palate, internal hydrocephalus, and truncus arteriosus communis.

Skeletal Examination: In the control, low-, and mid-dose groups, seven (five litters), nine (nine litters), and seven (six litters) fetuses, respectively, exhibited anomalies related to the sternum and vertebral column. In the high-dose group, three fetuses (three litters) showed anomalies related to the head and sternum. The incidences of variations and retardations were similar among all dose groups (data not shown). There was no significant difference between the individual test groups concerning fetuses with anomalies, variations, or retardations.

D. DISCUSSION/CONCLUSION:

1. Maternal Toxicity: Maternal toxicity, evidenced by reduced food consumption during the dosing period, reduced body weight gain during the first days of dosing, increased water consumption during the gestational period, and 3/22 dams with severe weight loss and ulceration of the glandular stomach leading to premature death, was observed only at the high-dose level (438 mg/kg/day). Since analysis of dosing solutions could not be confirmed due to lack of proper documentation, the maternal toxicity NOEL and LOEL were not determined.

TABLE 5. Summary of Fetal Anomalies[a]

Findings[b]	Dose Level (mg/kg/day) 0	24.4	146	438
No. fetuses (litters) examined externally	321 (25)	297 (25)	307 (23)	259 (20)
Kinky tail	1	0	0	0
Anasarca	0	0	0	1
No. fetuses (litters) examined viscerally[c]	321 (25)	297 (25)	307 (23)	259 (20)
Situs inversus	1	0	0	0
Microphthalmia	1	1	0	1
Anophthalmia	0	0	0	1
Cleft palate	0	0	0	1
Internal hydrocephalus	0	0	1	1
Truncus arteriosus communis	0	0	0	1
No. fetuses (litters) examined skeletally[d]	217 (25)	199 (25)	205 (23)	176 (20)
Thoracic vertebra body like a dumb-bell	2	4	4	0
Thoracic vertebra body bipartited	0	2	1	0
Brachygnathia inferior	0	0	0	1
Cleft palate	0	0	0	1
Lumbar vertebra body bipartited	3	1	3	2
Sternebrae bones dislocated	2	2	1	1

[a]Data were extracted from study No. 87/0167, Tables 16, 18, 24, 26, 30, 32, 36, and 38

[b]More than one type of anomaly may be found in one fetus.

[c]All fetuses were examined for soft tissue anomalies.

[d]Litter incidence could not be verified because of lack of individual fetal data.

2. Developmental Toxicity:

a. Deaths/Resorptions: The author reported that no compound-related deaths or resorptions were observed in any dose group. There were, however, nonsignificant increases in resorptions per dam from 1.2 in controls to 1.6 and 2.0, respectively, in the low- and high-dose groups. Likewise, there were nonsignificant increases in postimplantation loss from 8.23% in controls to 11.29% and 14.18%, respectively, in the low- and high-dose groups. Because these increases were not dose-dependent and reasonably close to the historical controls, they were not considered biologically relevant.

b. Altered Growth: A significant increase in fetal body weight was observed in all treated groups. This was considered to be incidental and not biologically relevant.

c. Developmental Anomalies: The number of litters with external anomalies (one control, one high-dose), visceral anomalies (one control, one low-dose, one mid-dose, two high-dose) and skeletal anomalies (four controls [reported by the author in the text as "five controls", but this should have been four according to the tables], nine low-dose, six mid-dose, three high-dose), was not statistically significantly different from controls; also there was no dose-related pattern. Among viscerally examined fetuses in the high-dose group, three of five anomalies occurred within one litter, indicating that there may have been a litter effect.

Based on these results, it was concluded that no developmental toxicity was present. However, since analysis of dosing solutions could not be confirmed because of lack of proper documentation, the developmental toxicity NOEL and LOEL were not determined.

3. Study Deficiencies:

a. Data to support concentration and stability analysis of dosing solutions were not provided.

b. Analysis of homogeneity of dosing solutions was not performed.

c. A statement of compliance with EPA GLPs was not submitted. The study was, however, conducted according to OECD GLPs. The only differences in requirements found in OECD GLPs were (1) a protocol is not presented in the study report, and (2) the length of time for storage of data are not specified.

E. CLASSIFICATION: CORE Supplementary Data.

Maternal NOEL = Not determined.
Maternal LOEL = Not determined.
Developmental Toxicity NOEL = Not determined.
Developmental Toxicity LOEL = Not determined.

F. RISK ASSESSMENT: Not applicable.

EPA No.: 68D80056
DYNAMAC No.: 247-B
TASK No.: 2-47B
February 28, 1990

DATA EVALUATION RECORD

QUINCLORAC

Two-Generation Reproductive Toxicity Study in Rats

STUDY IDENTIFICATION: Hellwig, J. Report on the reproduction study with Registration Number 150 732 in rats; continuous dietary administration over 2 generations (2 litters in the first and 1 litter in the second generation). (Unpublished study No. 88/0321 conducted by BASF Aktiengesellschaft, Federal Republic of Germany, and submitted by BASF Corporation, Chemicals Division, Parsippany, NJ; dated July 21, 1988.) MRID No. 410635-26.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature:

Date: 2/28/90

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EPA No.: 68D80056
DYNAMAC No.: 247-B
TASK No.: 2-47B
February 28, 1990

DATA EVALUATION RECORD

QUINCLORAC

Two-Generation Reproductive Toxicity Study in Rats

REVIEWED BY:

Patricia Turck, M.S.
Principal Reviewer
Dynamac Corporation

Signature: Patricia Turck
Date: February 28 1990

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Date: 4/12/90

DATA EVALUATION RECORD

STUDY TYPE: Reproductive Toxicity. Guideline §83-4.

MRID NUMBER: 410635-26.

TEST MATERIAL: 3,7-Dichloro-8-quinolinecarboxylic acid.

SYNONYMS: Registration No. 150 732, Quinclorac, Facet, BAS 514 00H.

STUDY NUMBER: 88/0321.

SPONSOR: BASF Corporation, Chemicals Division, Parsippany, NJ.

TESTING FACILITY: BASF Aktiengesellschaft, Federal Republic of Germany.

TITLE OF REPORT: Report on the Reproduction Study with Registration Number 150 732 in Rats; Continuous Dietary Administration Over 2 Generations (2 Litters in the First and 1 Litter in the Second Generation).

AUTHOR: Hellwig, J.

REPORT ISSUED : July 21, 1988.

CONCLUSIONS:

In a two-generation reproduction study in which rats were fed diets containing quinclorac at 0, 1,000, 4,000, or 12,000 ppm (approximately 50, 200, or 600 mg/kg/day, respectively), parental toxicity was observed at the high-dose level. Reduced body weight during the premating periods for both high-dose males and females and reduced maternal body weight during lactation were observed. In addition, increased incidences of interstitial nephritis were noted in high-dose females. The LOEL for parental toxicity is 12,000 ppm, and the NOEL is 4,000 ppm.

Fertility and length of gestation were unaffected by ingestion of the test material. However, pup viability, physical development (pinna unfolding, eye opening), and growth (reduced pup weight) were adversely affected at the high-dose level. Therefore, the LOEL for reproductive toxicity is 12,000 ppm, and the NOEL is 4,000 ppm.

Classification: CORE Supplementary Data. No data on the stability of the test material in the diet was presented. Therefore, the amount of test material consumed was not determined. This study can be upgraded if data on stability and individual animal data for food consumption and clinical observations are submitted.

A. MATERIALS:

Test Compound:
- Purity: 97.4% (batch No. N55 III); 98.3% (batch No. N57 III/2).
- Description: Colorless, crystalline solid.
- Lot No.: Not reported; batch Nos. N55 III and N57 III/2.
- Contaminants: Not reported.

Vehicle(s): None used; the test material was administered in the diet.

Test Animals:
- Species: Rat.
- Strain: Wistar [Chbb = THOM (SPF)].
- Source: Karl THOMAE, Biberach an Der Riss, Federal Republic of Germany.
- Age: Approximately 34 days at study initiation.
- Weight: F_0 Males--137-160 g and F_0 females --101-126 g; F_1 males--43-119 g and F_1 females--35-102 g at beginning of treatment period.

B. STUDY DESIGN:

This study was designed to assess the reproductive toxicity potential of quinclorac, when administered continuously in the diet for two successive generations.

Mating: After at least 70 days on the test diets, F_0 parental animals were mated 1:1 to produce the first litter (F_{1a}). Females were paired for a maximum of 3 weeks with the same males. Day 0 of gestation was designated as the day on which positive evidence of mating, i.e., presence of sperm in the vaginal smear, was observed. Approximately 10 days after weaning of the first litter, parental animals were again mated to produce a second litter (F_{1b}). Different pairings were utilized during the second mating.

F_1 parental animals were chosen from the F_{1a} litters after weaning. Mating was conducted approximately 98 days after initiation on the test diets. Pairing was conducted in a manner similar to that described above, except that F_1 parents were mated to produce one litter only (F_{2a}).

Animals from the F_0 and F_1 parental generations failing to produce a litter (males and females) were remated with proven (fertile) animals from the respective control groups to evaluate fertility. "Fertilized" females were subsequently sacrificed between gestational days (GD) 11 and 18, and unfertilized females were sacrificed 3 or 10 days after the last mating. Males were sacrificed 3 to 18 days after the last mating.

Group Arrangement: Animals were randomly allocated to groups according to body weight as follows:

Test group	Dietary Concentration (ppm)	Number assigned per group F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	24	24	24	24
Low dose	1,000	24	24	24	24
Mid dose	4,000	24	24	24	24
High dose	12,000	24	24	24	24

Dosing: The test material was administered continuously in the diet over two consecutive generations. The test diets were prepared every 2 weeks (as stated in protocol amendment No. 1

by thoroughly mixing the test material in a small portion of feed. Feed was then added to this premix to obtain desired concentrations of the test material. Stability and homogeneity of the test material in the feed were verified prior to study initiation and after study termination. Concentrations were analyzed at the beginning of the study and every 3 months thereafter. Selection of dietary levels was based on the results of two range-finding studies and a 90-day dietary study. In the 90-day study, animals received dietary levels of 1,000, 4,000, or 12,000 ppm. At 12,000 ppm, reductions in food consumption and body weight and elevations in water consumption were observed. In addition, several clinical chemistry and hematology parameters were affected in high-dose animals. The affected clinical chemistry parameters included increases in SGOT, SGPT, bilirubin, creatinine, urea, potassium, and albumin; and decreases in chloride, sodium, and alkaline phosphatase. The hematology parameters affected were reduced platelet and lymphocyte counts and increased neutrophil count. Chronic interstitial nephritis was observed in several high-dose males.

Observations: Animals were checked daily for mortality, moribundity, and clinical signs of toxicity (frequency during the day was not reported). Food consumption was measured twice a week (Monday and Friday). The body weight of males was measured weekly. The body weight of females was measured weekly during the premating period and daily during the mating periods. During gestation and lactation, maternal body weights were determined on GD 0, 7, 14, and 20 and days 0, 7, 14, and 20 postpartum.

The following data were recorded for each litter:

- Number of pups alive and dead at birth and daily throughout the lactation period;

- Sex and external anomalies of viable pups on day 0 of lactation;

- Daily observations for clinical signs of toxicity and external anomalies;

- Individual body weight of pups on days 0, 4, 7, 14, and 21 postpartum;

- Attainment of developmental landmarks, i.e., pinna unfolding (day 4 of lactation), opening of auditory canal (day 13), eye opening (day 16) of individual pups; and

- Results of behavioral tests, i.e., gripping reflex, pupillary reflex (two pups/sex/litter), auditory response (all pups), during the rearing period.

After weaning on day 21 postpartum, F_{1a} pups not chosen as F_1 parental animals, F_{1b} pups, F_{2a} pups and any pups stillborn or found dead during the study were subjected to a gross necropsy. Pups stillborn or found dead were examined for external abnormalities and eviscerated for examination of visceral abnormalities. Skeletal abnormalities were assessed using a modified method of Kimmel (1981). Any pups that exhibited skeletal changes during lactation were subjected to further examination that included x-ray of skeletons and evaluation of heads using Wilson's method.

After weaning of the second litter (F_{1b}) from the F_0 generation and the first litter (F_{2a}) from the F_1 generation, all parents were sacrificed and subjected to a gross necropsy with particular attention given to reproductive organs. The uteri of apparently nonpregnant animals were stained with 10% ammonium sulfide to detect early resorptions.

The following organs were fixed in 4% buffered formaldehyde:

- Vagina
- Cervix
- Uterus
- Ovaries
- Testes
- Epididymides
- Seminal vesicles
- Prostate
- Coagulation gland
- Pituitary
- Liver
- Kidneys
- All gross lesions

The above organs were histologically examined in all control and high-dose F_0 and F_1 parental animals. In addition, kidneys, liver, and gross lesions from low- and mid-dose F_0 and F_1 parents were histologically examined.

Statistical Analysis: The following parameters were analyzed using statistical methods listed below:

- Body weight, body weight gain, food consumption--William's test;
- Developmental milestones, gripping reflex, auditory test, pupillary reflex, number of live and dead pups at birth--Fisher's Exact test: and
- Numbers and percentages of live and dead pups at birth, viability index, lactation index, litter incidences of anomalies, variations and retardations--Krauth test (linear rank test).

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated February 20, 1989, was provided.

- A signed Statement of Compliance with EPA GLPs was not provided. This study was conducted in accordance with the Organization of Economic Cooperation and Development (OECD) GLPs.

- A Quality Assurance Statement, signed by R. Rossbacher and dated July 20, 1988, was provided.

C. RESULTS:

The study author reported the following results.

1. Test Material Analysis: The concentrations of the test diets were within acceptable ranges. The test diets were demonstrated to be homogeneous and stable for 30 days.

2. Parental Toxicity:

Mortality: One pregnant control F_1 female (No. 307) was sacrificed in a moribund condition approximately 19 weeks after initiation on the test diet (day 126). She was unable to deliver; macroscopic examination revealed torsion of the uterus with congestion and hemorrhagic swelling of the uterine wall.

Clinical Observations: No abnormal clinical observations were noted. However, no clinical observation data were presented.

Body Weight: Premating body weight is summarized in Table 1. Body weight was significantly reduced in high-dose F_1 females at weeks 15, 16, 24, and 26 when compared with controls. During the F_1 generation, the body weight of high-dose males and females was generally reduced during the entire premating period. F_1 males were significantly lighter at all measurement intervals. The body weight of high-dose F_1 females was significantly reduced at all intervals, except during weeks 6, 12, and 14-16.

Maternal body weight during gestation and lactation is summarized in Table 2. Maternal body weights were significantly reduced during gestation in F_1 females ($p < 0.05$) and during lactation in F_0 ($p < 0.01$) and F_1 ($p < 0.05$) females from the high-dose group when compared with controls.

Food Consumption: No differences in food consumption were observed in animals from the control and test groups during the premating period of the F_0 or F_1 generations. Reductions of 10-16% in food consumption at the high-dose level were observed in females during lactation (Table 3).

TABLE 1. Summary of Body Weight Data for Rats Fed Quinclorac in the Diet for Two Generations[a]

Dietary Concentration (ppm)	Mean Body Weight (± S.D.) at Study Week: 0	6	12	18	24
F$_0$ Males					
0	148 ± 5.1	366 ± 18.3	441 ± 31.5	496 ± 39.0	523 ± 43.1
1,000	148 ± 5.5	371 ± 20.4	450 ± 32.6	504 ± 43.5	531 ± 49.6
4,000	148 ± 5.1	372 ± 28.8	458 ± 40.1	516 ± 49.5	545 ± 56.2
10,000	148 ± 5.3	362 ± 24.1	444 ± 34.2	494 ± 38.3	531 ± 42.0
F$_0$ Females					
0	116 ± 5.2	231 ± 15.4	304 ± 21.4	295 ± 21.4	368 ± 30.3
1,000	116 ± 5.7	227 ± 17.2	307 ± 21.4	296 ± 18.3	373 ± 23.3
4,000	116 ± 5.1	225 ± 14.5	298 ± 17.6	290 ± 21.1	369 ± 25.0
10,000	117 ± 5.3	230 ± 22.9	296 ± 23.9	289 ± 21.4	352 ± 21.2*
F$_1$ Males					
0	76 ± 12.7	341 ± 25.1	443 ± 34.9	491 ± 39.7	-
1,000	79 ± 13.3	343 ± 28.4	446 ± 37.1	499 ± 40.1	-
4,000	74 ± 10.0	335 ± 29.5	436 ± 41.1	490 ± 48.4	-
10,000	58 ± 10.3**	308 ± 22.3**	412 ± 31.4**	463 ± 40.5*	-
F$_1$ Females					
0	70 ± 11.8	215 ± 15.1	265 ± 20.4	340 ± 52.5	-
1,000	72 ± 11.7	217 ± 22.8	265 ± 30.1	324 ± 51.9	-
4,000	68 ± 10.6	213 ± 17.9	262 ± 20.0	319 ± 43.7	-
10,000	53 ± 11.2**	204 ± 17.3	249 ± 22.0	299 ± 47.5**	-

[a] Data were extracted from study No. 38/032[illegible], Tables [illegible], 023-028, [illegible], [illegible], A2[illegible], and A4[illegible].

*Significantly different from controls ($p < 0.05$)

**Significantly different from controls ($p < 0.01$)

TABLE 2. Summary of Body Weight Data (g) During Gestation and Lactation for Female Rats Fed Quinclorac for Two Generations[a]

Dietary Concentration (ppm)	Gestational Day: 0	7	14	20	Lactational Day: 0	7	14	21
F_0 Females-First Mating								
0	268 ± 17.2[b]	292 ± 21.2	321 ± 23.9	384 ± 36.3	306 ± 24.1	319 ± 26.1	329 ± 23.3	314 ± 27.1
1,000	263 ± 19.9	290 ± 18.3	321 ± 18.0	384 ± 24.6	303 ± 20.8	320 ± 20.7	328 ± 19.3	315 ± 17.1
4,000	258 ± 20.8	282 ± 20.1	312 ± 18.5	377 ± 20.0	296 ± 21.3	314 ± 18.7	322 ± 17.7	310 ± 18.8
12,000	260 ± 21.3	281 ± 20.5	311 ± 21.8	273 ± 28.5	288 ± 25.1	301 ± 24.3	298 ± 26.4**	292 ± 23.5**
F_0 Females-Second Mating								
0	304 ± 21.4	325 ± 25.2	355 ± 27.0	437 ± 39.2	337 ± 24.5	341 ± 25.3	328 ± 26.8	322 ± 24.0
1,000	304 ± 18.5	329 ± 19.4	361 ± 21.7	440 ± 25.4	359 ± 28 5	358 ± 18.6	350 ± 25.9	339 ± 18.3
4,000	299 ± 22.0	318 ± 24.1	348 ± 26.3	426 ± 29.9	360 ± 23.1	365 ± 19.7	360 ± 25.4	346 ± 25.6
12,000	298 ± 20.4	317 ± 21.4	342 ± 21.9	409 ± 34.9**	345 ± 21.8	350 ± 18.6	341 ± 22.7	324 ± 30.9**
F_1 Females								
0	274 ± 20.9	299 ± 22.9	322 ± 20.4	380 ± 27.2	302 ± 18.1	325 ± 20.2	328 ± 22.2	322 ± 17.8
1,000	273 ± 25.0	298 ± 25.9	322 ± 26.3	280 ± 39.1	308 ± 27.6	327 ± 26.0	333 ± 26.3	323 ± 25.2
4,000	274 ± 21.5	298 ± 22.3	325 ± 22.4	385 ± 26.6	307 ± 25.1	331 ± 23.7	335 ± 22.7	326 ± 25.1
12,000	261 ± 23.5	284 ± 24.7	307 ± 30.0*	358 ± 42.5*	290 ± 26.8	305 ± 30.0*	310 ± 29.1*	306 ± 27.3*

[a]Data were extracted from Study No. 88/0321, Tables 035, 037, 039, 175, and 175.

[b]Mean ± S.D.

*Significantly different from controls ($p < 0.05$).

**Significantly different from controls ($p < 0.01$).

TABLE 3. Summary of Food Consumption Data (g/day) During Gestation and Lactation for Female Rats Fed Quinclorac for Two Generations[a]

Dietary Concentration (ppm)	Gestational Day Interval: 0-7	7-14	14-20	Lactational Day Interval: 0-7	7-14	14-21
F_0 Females-First Mating						
0	22 ± 2.8[b]	24 ± 2.5	26 ± 3.0	39 ± 4.3	61 ± 8.1	81 ± 10.1
1,000	24 ± 1.9	26 ± 2.1	27 ± 2.0	41 ± 5.6	62 ± 6.8	83 ± 10.9
4,000	22 ± 1.9	24 ± 1.8	26 ± 2.3	42 ± 4.1	62 ± 5.2	80 ± 5.2
12,000	22 ± 1.8	24 ± 1.7	26 ± 2.2	38 ± 7.5	53 ± 11.1	64 ± 16.1
F_0 Females-Second Mating						
0	25 ± 2.9	26 ± 2.5	28 ± 2.6	42 ± 6.7	65 ± 11.8	86 ± 15.6
1,000	27 ± 2.0	28 ± 1.9	28 ± 1.7	44 ± 4.4	66 ± 5.6	89 ± 9.6
4,000	25 ± 2.2	26 ± 2.2	28 ± 2.4	44 ± 4.7	66 ± 4.7	85 ± 8.8
12,000	25 ± 2.5	26 ± 2.6	27 ± 3.6	44 ± 3.6	63 ± 4.5	75 ± 8.7
F_1 Females						
0	23 ± 1.7	24 ± 1.6	24 ± 2.3	41 ± 7.4	63 ± 11.2	85 ± 16.7
1,000	23 ± 1.5	24 ± 1.4	25 ± 2.6	42 ± 5.1	65 ± 7.5	89 ± 11.7
4,000	23 ± 1.4	25 ± 1.3	25 ± 2.0	41 ± 6.1	62 ± 9.5	82 ± 12.7
12,000	23 ± 1.7	24 ± 2.0	24 ± 3.3	37 ± 8.1	56 ± 12.3	72 ± 16.4

[a]Data were extracted from Study No. 88/0321, Tables 007-010, 151-152, A007-010, and A402-403.

[b]Mean ± S.D.

However, statistical analysis was not performed on this parameter.

The calculated test material intake (mg/kg/day) was as follows:

	Dietary Concentration (ppm)		
	1,000	4,000	12,000
F_1 males	87.3	343.3	1026.3
F_1 females			
- premating	96.9	381.4	1155.0
- F_{1a} gestation	81.8	318.0	952.9
- F_{1b} gestation	78.3	307.5	914.2
F_2 males	94.0	379.8	1208.8
F_2 females			
- premating	104.6	420.3	1328.8
- F_{2a} gestation	76.8	306.6	944.0

Gross and Microscopic Pathology: Microscopic examination revealed an increased number of high-dose females with interstitial nephritis of the kidneys; 4, 1, 4, and 16 F_1 females and 6, 5, 4, and 17 F_2 females from the control, low-dose, mid-dose, and high-dose groups, respectively, were affected. Similar increases were not observed in high-dose males.

3. Reproductive Toxicity: The effects of the dietary administration of the test material on reproductive parameters and offspring survival are summarized in Tables 4 and 5. A significant increase in the number of live pups per litter at birth was observed after the first mating (F_{1a}) in the mid-dose group compared with controls. The litter size at birth (live and dead pups, combined) was significantly reduced after the second mating (F_{1b}) in the high-dose group when compared with controls. Slight, but not statistically significant, reductions in the viability and lactation indices were observed in high-dose F_{1a} pups during the entire lactation period when compared with controls.

Body weights of offspring are summarized in Table 6. Significant reductions in body weight were observed in F_{1a} ($p < 0.05$-0.01), F_{1b} ($p < 0.01$), and F_{2a} ($p < 0.05$-0.01) pups

TABLE 4. Summary of Effects of Dietary Administration of Quinclorac on F_0 Reproductive Parameters and Offspring Survival

Parameter	Dietary Concentration (ppm)							
	0		1,000		4,000		12,000	
	F_{1a}	F_{1b}	F_{1a}	F_{1b}	F_{1a}	F_{1b}	F_{1a}	F_{1b}
No. Matings	24	24	24	24	24	24	24	24
No. Pregnancies	23	24	23	24	23	24	23	22
Female Fertility Index (%)	95.8	100.0	95.8	100.0	95.8	100.0	95.8	91.7
Pregnancy Index (%)[b]	100.0	95.8	100.0	100.0	100.0	100.0	95.7	100.0
Mean Gestation Length (days)	22.3	22.2	22.3	22.2	22.3	22.1	22.3	22.1
Total No. Pups Born	289	351	279	337	298	346	291	295
Mean Litter Size at Birth	12.6	14.6	12.1	14.0	13.0	14.4	12.7	13.4
Total No. Pups Alive, Day 0	266	339	278	331	287	338	284	287
Mean No. Live Pups/Litter	12.4	14.1	12.1	13.8	12.5*	14.1	12.4	13.0
Total No. Pups Alive, Day 4	277	331	272	322	281	336	268	285
Mean No. Live Pups/ Litter	12.0	13.8	11.8	13.4	12.2	14.0	11.7	12.9
Viability Index (%)[c]	96.4	97.9	97.8	97.6	97.9	99.4	94.0	99.3
Total No. Pups Alive, Day 21	275	326	265	313	278	330	256	282
Mean No. Live Pups/Litter	12.0	13.6	11.5	12.9	12.1	13.8	11.1	12.8
Lactation Index (%)[d]	99.4	98.4	97.6	96.8	99.0	98.5	95.5	99.3
Survival Rate (%)[e]	95.8	96.3	95.4	94.5	97.0	98.0	89.6	97.2

[a]Data were extracted from study No. 58/0321, Tables 069-072 and 118-129.

[b]This parameter is usually defined as gestation index.

[c]Viability Index = $\frac{\text{No. pups alive per litter on Day 4}}{\text{No. pups alive per litter at birth}} \times 100.$

[d]Lactation Index = $\frac{\text{No. pups alive per litter on Day 21}}{\text{No. pups alive per litter on Day 4}} \times 100.$

[e]Survival Rate = $\frac{\text{No. pups alive per litter on Day 21}}{\text{No. pups alive per litter at birth}} \times 100.$

*Significantly different from controls ($p < 0.05$).

TABLE 5. Summary of Effects of Dietary Administration of Quinclorac on F$_1$ Reproductive Parameters and Offspring Survival[a]

Parameter	Dietary Concentration (ppm)			
	0	1,000	4,000	12,000
No. Matings	24	24	24	24
No. Pregnancies	22	19	24	23
Female Fertility Index (%)	95.8	83.3	100.0	95.8
Pregnancy Index (%)[b]	100.0	100.0	100.0	100.0
Mean Gestation Length (days)	22.6	22.3	22.4	22.3
Total No. Pups Born	283	254	288	282
Mean Litter Size at Birth	12.9	13.4	12.0	12.3
Total No. Pups Alive, Day 0	275	251	274	269
Mean No. Live Pups/Litter	12.5	13.2	11.4	11.7
Total No. Pups Alive, Day 4	260	236	267	25*
Mean No. Live Pups/Litter	11.8	12.4	11.1	10.9
Viability Index (%)[c]	90.9	95.3	97.7	92.2
Total No. Pups Alive, Day 21	258	235	266	246
Mean No. Live Pups/Litter	11.7	12.4	11.1	10.7
Lactation Index (%)[d]	99.3	99.7	99.7	96.4
Survival Rate (%)[e]	90.3	94.7	97.5	88.6

[a]Data were extracted from study No. 88/0321, Tables 193-194 and 219-224.

[b]This parameter is usually defined as gestation index.

[c]Viability Index = $\frac{\text{No. pups alive per litter on Day 4}}{\text{No. pups alive per litter at birth}} \times 100.$

[d]Lactation Index = $\frac{\text{No. pups alive per litter on Day 21}}{\text{No. pups alive per litter on Day 4}} \times 100.$

[e]Survival Rate = $\frac{\text{No. pups alive per litter on Day 21}}{\text{No. pups per litter alive at birth}} \times 100.$

TABLE 6. Summary of Body Weight Data for Offspring of Rats Fed Quinclorac in the Diet for Two Generations[a]

Dietary Concentration (ppm)	Mean Body Weight (g) on Lactational Day: 0	7	14	21
F1a Males				
0	6.1	14.1	26.9	44.9
1,000	6.3	14.2	27.3	46.4
4,000	6.2	14.2	26.1	41.9[b]
12,000	5.9	12.5*	22.5**	33.2**
F1a Females				
0	5.8	13.6	25.8	42.7
1,000	6.0	13.5	26.0	43.7
4,000	5.9	13.6	25.3	40.7
12,000	5.6	12.0	21.8**	31.8**
F1b Males				
0	6.0	13.3	24.9	42.3
1,000	6.1	13.9	26.[illegible]	44.9
4,000	6.2	13.6	25.3	40.9
12,000	6.0	13.3	24.3	35.3**
F1b Females				
0	5.[illegible]	12.[illegible]	[illegible]	40.3
1,000	5.9	13.3	25.6	42.3
4,000	5.8	12.9	24.4	39.3
12,000	5.8	13.1	23.9	34.6**
F2a Males				
0	6.1	15.1	28.3	47.9
1,000	6.0	14.9	28.3	47.2
4,000	6.2	15.5	28.9	47.9
12,000	5.7*	12.7**	24.3*	37.2**
F2a Females				
0	5.9	14.7	27.3	45.7
1,000	5.6	14.1	27.1	45.2
4,000	5.9	15.1	28.2	45.7
12,000	5.5*	12.8*	24.2*	37.3**

[a]Data were extracted from study No. 88-0321, Tables 074, 075, 078, 080, and 199.

[b]Recalculated by the reviewers; the study author reported a value of 42

*Significantly different from controls ($p < 0.05$).

**Significantly different from controls ($p < 0.01$).

from the high-dose group. Reductions began on day 7 postpartum in F_{1a} males, day 14 postpartum in F_{1a} females, and at birth for both F_{2a} males and females. Reduced body weight was observed in F_{1b} pups on day 21 postpartum.

Developmental landmarks are summarized in Table 7. Significant developmental delays were observed in high-dose F_{1a} pups for eye opening, pinna unfolding, and auditory canal opening and in high-dose F_{2a} pups for eye opening and auditory canal opening.

D. REVIEWERS' DISCUSSION/CONCLUSIONS:

1. Test Material Analysis: The stability analysis data collected prior to study initiation were from the year 1983. The test material concentration reported for this test was 42 mg/kg (equivalent to 42 ppm). Since the dietary concentrations used in the present study were much higher, the usefulness of these data is questionable. The author stated that verification of the stability was performed after termination of the study, but these data were not presented. An analytical report entitled "Stability Control," which states that analysis was conducted on March 5, 1988, is presented. However, it is unacceptable because number of days for which the stability test was conducted was not reported. Also, this test was not performed on the test diets, but on the technical sample (N57 III/2) only.

   Concentration analyses were conducted prior to study initiation and every 3 months (a total of three analyses) thereafter, as specified in the protocol. However, the last two analyses (for batch No. N57 III/2) included the mid-dose group only; no results were presented for the low- or high-dose groups (1,000 and 12,000 ppm, respectively). Actual concentrations ranged from 96 to 117% of target concentrations for the first two analyses (batch No. N55 III).

2. Parental Toxicity: Significant reductions in body weight during the premating period, particularly in the F_1 generation, were observed in high-dose males and females. Furthermore, maternal body weights were significantly reduced during the latter part of lactation at the high-dose level. Maternal food consumption for high-dose animals was slightly reduced during the latter part of lactation. Unfortunately, the reviewers could not conduct statistical analysis because individual animal data were not presented. The incidence of mild interstitial nephritis was higher in high-dose F_0 and F_1 females than

TABLE 7. Summary of Effects of Dietary Administration of Quinclorac on the Development of Offspring (Males + Females)

Developmental Landmark	Dietary Concentration (ppm) 0	1,000	4,000	12,000
F_{1a} Pups				
Pinna Unfolding (%)[b]	98.6	99.6	98.9	91.4**
Auditory Canal Opening (%)[c]	94.2	97.4	97.8	87.9*
Eye Opening (%)[d]	100.0	100.0	100.0	97.3*
F_{1b} Pups				
Pinna Unfolding (%)	100.0	100.0	100.0	100.0
Auditory Canal Opening (%)	96.9	98.1	97.3	98.6
Eye Opening (%)	100.0	100.0	100.0	100.0
F_{2a} Pups				
Pinna Unfolding (%)	100.0	100.0	100.0	100.0
Auditory Canal Opening (%)	100.0	97.5*	99.6	91.1**
Eye Opening (%)	100.0	99.6	99.3	95.5**

[a]Data were extracted from study No. 88/0321, Tables 084, 087, 090, 093, 096, 099, 203, 206, and 209.

[b]Represents the percentage of pups/group achieving pinna unfolding by Day 4 postpartum.

[c]Represents the percentage of pups/group achieving auditory canal opening by Day 13 postpartum.

[d]Represents the percentage of pups/group achieving eye opening by Day 16 postpartum.

*Significantly different from controls ($p < 0.05$).

**Significantly different from controls ($p < 0.01$).

controls: 4, 1, 4, and 16 F_0 females and 6, 5, 4, and 17 F_1 females from the control, low-dose, mid-dose, and high-dose groups, respectively, were affected. Similar increases, however, were not seen in males.

Based on these results, the LOEL for parental toxicity is 12,000 ppm, and the NOEL is 4,000 ppm.

3. Reproductive Toxicity: Fertility, pregnancy rates, and length of gestation were unaffected by ingestion of the test material. However, pup viability at the high-dose level (F_{1b} generation) was reduced when compared with controls. In addition, body weights of high-dose pups, particularly following the F_1 mating, were significantly reduced, and developmental delays, i.e., pinna unfolding and eye opening, were evident at the high-dose level when compared with controls. Approximately 9% of high-dose F_{1a} and F_{2a} pups failed to achieve pinna unfolding by day 4 postpartum as compared to 1% of controls. For eye opening, 3-5% of high-dose F_{1a} and F_{2a} pups failed to achieve this landmark by day 16 postpartum as compared to 0% for controls.

Based on these results, the LOEL for reproductive toxicity is 12,000 ppm, and the NOEL is 4,000 ppm.

4. Study Deficiencies: The following deficiencies were noted.

a. Data on stability analyses of the test material in feed at the levels tested were not presented. Data on concentration analyses were incomplete.

b. Culling of litters on day 4 postpartum was not conducted.

c. Statistical analysis of food consumption was not performed. The reviewers could not conduct statistical analysis because individual animal data were not presented.

d. Clinical observation data were not presented.

e. This study was conducted according to OECD GLPs and not USEPA GLPs. The only difference between the two appears to be the amount of time required for storage of data (paper and tissues). This should be clarified in the study report.

E. CLASSIFICATION: CORE Supplementary Data.
Parental NOEL = 4,000 ppm (approximately 350 mg/kg/day).[1]
Parental LOEL = 12,000 ppm (approximately 1076 mg/kg/day).[1]
Reproductive Toxicity NOEL = 4,000 ppm.
Reproductive Toxicity LOEL = 12,000 ppm.

F. RISK ASSESSMENT: Not applicable.

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[1]Calculated by the reviewers as mean test material intake of F_2 and F_1 males and females during the premating and gestation periods only. The test material intake during lactation was excluded because pups probably ingested food also. This created higher test material intake values since they were calculated using maternal body weight only.

EPA No.: 68D80056
DYNAMAC No.: 247-E
TASK No.: 2-47E
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Salmonella typhimurium Microsome Mammalian Mutagenicity Assay

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: [signature]

Date: 12-5-89

This study has been upgraded to Acceptable (see Document #).

EPA No.: 68D80056
DYNAMAC No.: 247-E
TASK No.: 2-47E
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--*Salmonella typhimurium* Microsome Mammalian Mutagenicity Assay

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DATA EVALUATION RECORD

CHEMICAL: Quinclorac.

STUDY TYPE: Mutagenicity--Salmonella typhimurium mammalian microsome mutagenicity assay.

ACCESSION/MRID No.: 410635-27.

TEST MATERIAL: Registration No. 150 732.

SYNONYMS/CAS No.: 3,7-Dichloro-8-quinolinecarboxylic acid; BAS 514 H.

SPONSOR: BASF Corporation Chemical Division, Parsippany, NJ.

TESTING FACILITY: BASF Aktiengesellschaft, Ludwigshafen, W. Germany.

TITLE OF REPORT: Report on the Study of Reg. No. 150 732 in the Ames Test (Standard Plate Test with Salmonella typhimurium) Dated May 4, 1984.

AUTHOR(S): Engelhardt, G.

STUDY No(s).: 84/0156.

REPORT ISSUED: May 4, 1984.

CONCLUSION(S)/EXECUTIVE SUMMARY: Two independent Salmonella typhimurium mammalian microsome mutagenicity assays were conducted with five concentrations of the test material, Registration (Reg.) No. 150 732, ranging from 20 to 5000 µg/plate. Although the test material failed to induce a mutagenic response in Salmonella typhimurium TA1535, TA1537, TA98, or TA100, the S9-activated assays were conducted with an excessive concentration of S9 (30%) in the S9 reaction mixture. Unless the author can justify the use of a high S9 concentration, the assay should be repeated using the recommended screening concentration (4% S9 in the S9 mix). Additionally, the purity of the test material was not reported and analytical data to support the actual concentrations of the test material that were used in the assay were not provided.

Study Classification: The study is unacceptable.*

A. MATERIALS:

1. Test Material:

Name:	Reg. No. 150-732-BAS 514, H
Description:	The physical appearance of the test material was not provided; however, the chemical name and structure were reported
Lot #:	84/150
Purity:	Listed as the technically active ingredient
Contaminants:	None listed
Solvent used:	Dimethylsulfoxide (DMSO)
Other comments:	The test material was stored at 4°C and was found to be completely soluble in DMSO up to 5000 µg/plate.

2. Control Materials:
Negative: DMSO
Solvent/final concentration: 100 µg/plate
Positive: Nonactivation:
N-methyl-N'-nitro-N-nitrosoguanidine 5 µg/plate TA100, TA1535
4-Nitro-o-phenylenediamine 10 µg/plate TA98
9-Aminoacridine 100 µg/plate TA1537

Activation:
2-Aminoanthracene (2AA) 10 µg/plate all strains.

3. Activation: S9 derived from

x	Aroclor 1254	x	induced	x	rat	x	liver
_____	phenobarbital	_____	noninduced	_____	mouse	_____	lung
_____	none			_____	hamster	_____	other
_____	other			_____	other		

* This study has been upgraded to Acceptable (see document #).

If other, describe below. Describe S9 composition (if purchased, give details). The S9 mix contained 30% S9 liver homogenate.

4. Test Organism Used: S. typhimurium strains
_____ TA97 __X__ TA98 __X__ TA100 _____ TA102 _____ TA104
__X__ TA1535 __X__ TA1537 _____ TA1538; list any others: _____.

Test organisms were properly maintained: YES
Checked for appropriate genetic markers (rfa mutation, R factor): YES.

5. Test Compound Concentrations Used:

Nonactivated conditions: 20, 100, 500, 2500, and 5000 µg/plate

Activated conditions: As above.

B. TEST PERFORMANCE:

1. Type of Salmonella Assay: __X__ Standard plate test
_____ Pre-incubation (___) minutes
_____ "Prival" modification
_____ Spot test
_____ Other (describe).

2. Preliminary Assay: A preliminary cytotoxicity assay was not performed.

3. Mutagenicity Assay: Five doses of the test material ranging from 20 to 5000 µg/plate were tested in two independent nonactivated and S9-activated plate incorporation assay. In the initial assay, the nonactivated test material was neither cytotoxic nor mutagenic (Table 1). Although a marked decrease in revertant colonies of strain TA100 was observed at S9-activated doses of 2500 and 5000 µg/plate, a similar reduction was not seen in the independently repeated assay (Table 2). No appreciable increase in reversion to histidine prototrophy of any strain resulted from exposure to the five selected nonactivated or S9-activated doses in either assay. The sensitivity of the test system to detect the mutagenic action of the nonactivated positive controls was clearly demonstrated. Although all strains responded to the mutagenic action of the S9-activated positive control (10 µg/plate 2AA), both the concentration of 2AA that was used and the percentage of S9 in the S9-cofactor mix (30%) were considerably higher than the levels generally required to show assay sensitivity.

TABLE 1. Representative Results of the Initial Plate Incorporation Salmonella typhimurium Mutagenicity Assay with Reg. No. 150 732

Substance	S9 Activation	Dose plate (µg/plate)	Revertents per Plate of Bacterial Tester Strain[a] TA1535	TA1537	TA98	TA100
Negative Control						
Dimethylsulfoxide	-	--	12 ± 1	7 ± 1	28 ± 1	107 ± 4
	+	--	18 ± 3	7 ± 1	46 ± 8	104 ± 2
Positive Controls[b]						
MNNG	-	5	1497 ± 199	--	--	2317±76
4NPA	-	10	--	--	860 ± 44	--
9AA	-	100	--	936 ± 105	--	--
2AA	+	10	473 ± 61	192 ± 20	1413 ± 93	2117±76
Test Material						
Reg. No. 150 732	-	5000[c]	13 ± 6	3 ± 1	23 ± 6	98 ± 15
	+	500	12 ± 4	11 ± 4	47 ± 11	101 ± 9
	+	2500	11 ± 3	9 ± 2	38 ± 7	92 ± 14
	+	5000[c]	7 ± 3	8 ± 5	39 ± 2	24 ± 8

[a]Means and standard deviations of counts from triplicate plates.

[b]Abbreviations used:
MNNG - N-Methyl-N'-nitro-N-nitrosoguanidine.
4NPA - 4-Nitro-o-phenylediamine
9AA - 9-Aminoacridine
2AA - 2-Aminoanthracene.

[c]Results for lower nonactivated (20, 100, 500, and 2500 µg/plate) and lower S9-activated (20 and 100 µg/plate) doses were generally comparable to the appropriate control values.

TABLE 2. Representative Results of the Repeat Plate Incorporation Salmonella typhimurium Mutagenicity Assay with Reg. No. 150 732

Substance	S9 Activation	Dose plate (µg/plate)	Revertants per Plate of Bacterial Tester Strain[a] S. typhimurium TA1535	TA1537	TA98	TA100
Negative Control						
Dimethylsulfoxide	-	--	16 ± 2	7 ± 1	29 ± 4	100 ± 4
	+	--	16 ± 2	10 ± 2	38 ± 6	132 ± 7
Positive Controls[b]						
MNNG	-	5	1713 ± 139	--	--	1347 ± 172
4NPA	-	10	--	--	706 ± 51	--
9AA	-	100	--	630 ± 30	--	--
2AA	+	10	288 ± 33	217 ± 14	1270 ± 44	1720 ± 131
Test Material						
Reg. No. 150 732	-	5000[c]	17 ± 3	6 ± 1	22 ± 5	92 ± 9
	+	5000	12 ± 2	8 ± 2	39 ± 7	96 ± 11

[a]Means and standard deviations of counts from triplicate plates.

[b]Abbreviations used:
MNNG - N-Methyl-N'-nitro-N-nitrosoguanidine
4NPA - 4-Nitro-o-phenylediamine
9AA - 9 Aminoacridine
2AA - 2-Aminoanthracene.

[c]Results for lower doses (20, 100, 500, and 2500 µg/plate with or without S9 activation) were generally comparable to the appropriate control values.

From the combined results of the two assays, the study author concluded that Reg. No. 150 732 was not mutagenic in this test system.

C. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

We assess that the results of the two independently performed S. typhimurium reverse mutation assays with the test material, Reg. No. 150 732, did not suggest a positive effect. However, the use of 30% S9 as the primary screening concentration is not recommended[1] and may have compromised the sensitivity of the system to detect a potential promutagen. It is possible for a promutagen to be deactivated and/or be detoxified by high mixed-function oxidase enzyme levels. Although conversion of the promutagen 2AA to an active mutagenic metabolite was demonstrated, the dose of 2AA (10 µg/plate) was higher than is conventionally applied. Using the recommended concentration of S9 in the S9 mix (4%), peak mutagenic activity of 2AA can be achieved at doses ranging from 0.5 to 2.5 µg/plate. It is not clear whether this high level of 2AA was required because of the excessive amount of S9 in the activation mix. We conclude, therefore, that unless the biochemical characteristics of the test material indicate a requirement for high enzyme levels, the use of 30% S9 as the primary screening concentration is not an acceptable practice.

D. QUALITY ASSURANCE MEASURES:

A quality assurance (QA) inspection of this study was not performed; however, a signed and dated (March 21, 1989) statement indicated that the data were valid and the outcome of the study was not affected by the lack of a QA inspection.

E. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 0011-0017.

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[1]Maron, M., and Ames, B.N. Revised methods for the Salmonella mutagenicity test. Mutat. Res. 113(1983): 173-215.

APPENDIX A
Materials and Methods
CBI pp. 0011-0017

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Pages 184 through 189 are not included.

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____ Identity of product inert ingredients.

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____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

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EPA No.: 68D80056
DYNAMAC No.: 247-I
TASK No.: 2-47I
December 7, 1989

CC[illegible]N
[illegible]

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Unscheduled DNA Synthesis in
Primary Rat Hepatocytes

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: [signature]

Date: 12-6-89

This study has been upgraded to Acceptable (see Document #).

190

EPA No.: 68D80056
DYNAMAC No.: 47-I
TASK No.: 2-47I
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Unscheduled DNA Synthesis in Primary Rat Hepatocytes

REVIEWED BY:

Nancy E. McCarroll, B.S.
Principal Reviewer
Dynamac Corporation
Signature: Nancy E. McCarroll
Date: 12-7-89

I. Cecil Felkner, Ph.D.
Independent Reviewer
Dynamac Corporation
Signature:
Date:

APPROVED BY:

Roman J. Pienta, Ph.D.
Department Manager
Dynamac Corporation
Signature:
Date: 12-6-89

William Greear, M.P.H.
EPA Reviewer, Section II
Toxicology Branch I
(H-7509C)
Signature:
Date: 12/1/89

Marion Copley, D.V.M., D.A.B.T.
EPA Section Head, Section II
Toxicology Branch I
(H-7509C)
Signature:
Date: 12/8/89

DATA EVALUATION RECORD

STUDY TYPE: Quinclorac.

STUDY TYPE: Mutagenicity--Unscheduled DNA synthesis in primary rat hepatocytes.

MRID/ACCESSION NUMBER: 410635-31.

TEST MATERIAL: Registration No. 150 732.

SYNONYM(S)/CAS NO.: 3,7-Dichloro-8-quinolinecarboxylic acid; ZNT No. 84/150; BAS 514 H.

SPONSOR: BASF Corporation Chemical Division, Parsippany, NJ.

TESTING FACILITY: Litton Bionetics, Inc., Kensington, MD.

TITLE OF REPORT: Report on the evaluation of Registration Number 150 732 (ZNT No. 84/150) in the *in vitro* rat primary hepatocyte unscheduled DNA assay, dated June 1986.

AUTHOR: Cifone, M.A.

STUDY NUMBER: 86/0135.

REPORT ISSUED: June 1986.

CONCLUSIONS/EXECUTIVE SUMMARY: Under the conditions of the assay, six doses ranging from 101 to 1520 µg/mL of test material, No. 150 732, did not induce an appreciable increase in the net nuclear grain counts of treated rat hepatocytes. Cytotoxicity was clearly demonstrated at concentrations ≥1520 µg/mL. It is concluded, therefore, that the test material is inactive in the primary rat hepatocyte unscheduled DNA synthesis (UDS) assay. However, the lack of information on test material purity and of supporting analytical data to confirm actual test material concentrations in solution precludes full acceptance of the study.

Study Classification:* The study is currently unacceptable but can be upgraded if the missing test material information can be supplied by the sponsor.

A. MATERIALS:

1. Test Material:

Name:	Reg. No. 150 732 (ZNT No. 84/150)
Description:	Off-white powder
Batch No.:	Not provided
Purity:	Reported to contain the technically active ingredient; purity (%) not provided.
Contaminants:	None listed
Solvent used:	Dimethylsulfoxide (DMSO)
Other comments:	The test material was reported to be stable in DMSO for at least 4 days. The test material formed a cloudy white suspension in DMSO at ≈300 mg/mL; a clear tan solution was achieved at 200 mg/mL. Stock solutions were prepared immediately prior to use.

2. Indicator Cells: Primary rat hepatocytes were obtained by the in situ perfusion of the liver of an adult male Fischer 344 rat (150-300 g) purchased from Charles River Breeding Laboratories, Inc.

3. Cell Preparation:

   a. Perfusion Technique: The liver was perfused with Hanks' balanced salts solution containing 0.5 mM EGTA and Hepes buffer, pH 7.0, for 4 minutes and with 50-100 u/mL collagenase in Williams' Medium E (WME) for 10 minutes. The liver was excised, removed to a culture dish containing WME and collagenase, and mechanically dispersed to release the hepatocytes.

* This study has been upgraded to Acceptable (see Document ###).

b. Hepatocyte Harvest/Culture Preparation: Recovered cells were centrifuged, resuspended in WME containing serum and dexamethasone, counted, and aliquoted (0.5×10^6 cells/3 mL WME) onto plastic coverslips. The cultures were placed in a humidified, 37°C, 5% CO_2 incubator for a 1.5- to 2-hour attachment period. Unattached cells were removed; viable cells were refed and established as monolayer cultures.

4. Positive Control: To demonstrate assay sensitivity to detect UDS, 0.05 µg/mL 2-acetylaminofluorene (2-AAF) was included as the positive control chemical.

B. STUDY DESIGN:

1. Dose Selection: Initially, 15 concentrations of the test material were assayed (1000-0.025 µg/mL in dilutions of approximately twofold steps). When the viability estimate was obtained (20-24 hours after treatment initiation), at least six of these doses were chosen for analysis of nuclear labeling, starting with the highest dose that resulted in a sufficient number of cells with intact morphologies and proceeding to successively lower doses.

2. UDS Assay:

a. Treatment: Five replicate, monolayer cultures were exposed to the selected doses of the test material, negative control (DMSO) or positive control (2-AAF, 0.05 µg/mL) for 18-19 hours in WME containing 1 µCi/mL [^{3}H]thymidine. Treated monolayers were washed twice with WME; two of the five replicates for each treatment group were used to determine cytotoxicity. These cultures were refed, reincubated, and monitored for cytotoxicity at 20-24 hours posttreatment by trypan blue exclusion.

b. UDS Slide Preparation: The remaining cultures were washed with medium containing 1 mM thymidine. Treated hepatocytes, attached to coverslips, were exposed to 1% sodium citrate for 8-10 minutes, fixed in acetic acid:ethanol (1:3), dried, and mounted.

c. Preparation of Autoradiographs/Grain Development: Slides were coated with Kodak NTB2 emulsion, dried for 7-10 days at 4°C in light-tight desiccated boxes, developed in Kodak D-19, fixed, stained with Williams' modified hematoxylin and eosin, coded, and counted.

d. Grain Counting: The nuclear grains of 150 morphologically normal cells for each test dose and negative and positive controls were counted microscopically. Net nuclear grain counts were determined by subtracting the nuclear grain counts of each cell from the mean cytoplasmic grain count of three nuclear-sized areas adjacent to each nucleus.

B. Evaluation Criteria:

a. Assay Validity: For the assay to be considered valid the following criteria must be satisfied: 1) hepatocytes recovered from the perfusion step and monolayer cultures used for the assay must show ≥70% viability; 2) the solvent controls should have net nuclear grain counts of ≤2; 3) the positive control must demonstrate the sensitivity of the test system to detect UDS; 4) data must be obtained from at least two replicate cultures/dose; and 5) the highest dose must show cytotoxicity, the limit of solubility, or reach the maximum recommended dose for this assay (5000 µg/mL).

b. Positive Response: The assay was considered positive if a) an increase in the mean nuclear grain count was ≥6 grains/nucleus over the negative control value, b) the percent of nuclei with ≥6 grains exceeded 10 percent of the negative control population, or c) the percent of nuclei with ≥20 grains was ≥2% of the examined population.

C. REPORTED RESULTS:

1. UDS Assay: Four trials were conducted. The report stated that the first trial was repeated to achieve "higher toxicities"; the dose range used in the first assay was not reported. Owing to unspecified technical problems, the second and third trials were aborted. For trial 4, eight concentrations ranging from 101 to 3040 µg/mL were assayed. The study author stated that compound precipitation was observed in the culture medium containing 759 to 3040 µg/mL of the test material; doses below 759 µg/mL (506 to 101 µg/mL) appeared to be fully soluble. The study author also noted that concentrations ≥253 µg/mL caused an acidic change in the pH of the culture medium; there was no indication that the pH was adjusted to compensate for the acidic condition caused by the test material. Results from the cytotoxicity assessment indicated that the two highest doses (2020 and 3040 µg/mL) were completely cytotoxic. Survival for the remaining levels ranged from 32.3% at 1520 µg/mL to 94.7% at 101 µg/mL. Based on these data, six doses (101, 253, 506, 759, 1010, and 1520 µg/mL) were scored for UDS.

As shown in Table 1, nuclear grain counts for the selected doses were generally comparable to the solvent control value. By contrast, the positive control, 0.05 µg/mL 2AAF, induced marked increases in UDS grains per nucleus and the percent nuclei with ≥6 grains. An appendix to the final report, dated June 1986, indicated that the stability of the test material in DMSO and in an aqueous medium was established analytically by the sponsor; no data were provided to support this statement.

Based on the overall results, the study author concluded, "The test material, ZNT No. 84/150, did not induce significant changes in the nuclear labeling of primary rat hepatocytes for an applied concentration range of 1520 µg/mL to 101 µg/mL."

D. REVIEWERS' DISCUSSION/INTERPRETATION OF STUDY RESULTS:

We assess that the study was conducted properly and that the author's interpretation of the data was correct. None of the doses induced an appreciable increase in UDS. The cytotoxic effect demonstrated at doses ≥1520 µg/mL indicated that the test substance entered the hepatocytes and that the lack of response was not due to the inability of the test material to penetrate the cell wall. The study adequately demonstrated both the solubility limits and cytotoxicity of the test material. Similarly, the ability of the test system to detect UDS was clearly shown by the findings with the positive control (2-AAF, 0.05 µg/mL). Although twice the number of cells were scored in the positive control group than was required by protocol, the applied concentration of 2-AAF was relatively low, hence providing added assurance of assay sensitivity. We conclude, therefore, that test material, Reg. No. 150 [illegible], failed to induce a genotoxic response in a well-controlled study. However, the lack of information on test material purity and of supporting data to confirm actual test material concentrations in solution renders the study unacceptable.

E. QUALITY ASSURANCE MEASURES: A quality assurance statement was signed and dated June 6, 1986.

F. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 0012-0018.

TABLE 1. Representative Results of the Unscheduled DNA Synthesis in Rat Hepatocyte Assay with Test Material, Reg. No. 150 732

Treatment	Dose	Cells Scored	Percent Survival[a] (23 Hours)	Average Nuclear Grain Count	Average Percent Nuclei w/ ≥6 Grains	Average Percent Nuclei w/ ≥20 Grains
Solvent Control						
Dimethylsulfoxide	1%	150	100.0	0.79	0.0	0.0
Positive Control						
2-Acetylamino-fluorene	0.05 µg/mL	300	100.7	6.80[b]	54.3[b]	2.0
Test Material						
Reg. No. 150 732	1010 µg/mL[c]	150	73.4	0.82	0.0	0.0
	1520 µg/mL[d]	150	32.3	0.18	0.0	0.0

[a] % Survival = $\frac{\text{No. of viable cells/unit area test dose}}{\text{No. of viable cells/unit area solvent control}} \times 100$.

[b] Fulfills reporting laboratory's criteria for a positive effect.

[c] Results for lower concentrations (101, 253, 506, and 759 µg/mL) were comparable to the solvent control, and, therefore, not presented.

[d] Highest dose scored; higher concentrations (2020 and 3040 µg/mL) were completely cytotoxic.

APPENDIX A

Materials and Methods

CBI pp. 0012-0018.

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EPA No.: 68D80056
DYNAMAC No.: 247-D
TASK No.: 2-47D
December 7, 1989

[redacted]
[redacted] INFORMATION [EO 12065]

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--In vitro Cytogenetic Assay with Human Lymphocytes

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: [redacted]

Date: 12/7/89

107

206

EPA No.: 68D80056
DYNAMAC No.: 247-D
TASK No.: 2-47D
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--*In vitro* Cytogenetic Assay with Human Lymphocytes

REVIEWED BY:

Nancy E. McCarroll, B.S.
Principal Reviewer
Dynamac Corporation
Signature: Nancy L McCarroll
Date: 12-7-89

I. Cecil Felkner, Ph.D.
Independent Reviewer
Dynamac Corporation
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APPROVED BY:

Roman Pienta, Ph.D.
Department Manager
Dynamac Corporation
Signature: Roman Pienta
Date: 12-7-89

William Greear, M.P.H.
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Marion Copley, D.V.M.,
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EPA Section Head,
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(H-7509C)
Signature: Marion Copley
Date: 1/3/90

DATA EVALUATION RECORD

CHEMICAL: Quinclorac.

STUDY TYPE: Mutagenicity--In vitro cytogenetic assay with human lymphocytes.

MRID/ACCESSION NUMBER: 410761-03.

TEST MATERIAL: Registration No. 150 732.

SYNONYM/CAS NO. 3,7-Dichloro-8-quinolinecarboxylic acid; BAS 51[illegible] H.

SPONSOR: BASF Corporation Chemical Division, Parsippany, NJ.

TESTING FACILITY: BASF Aktiengesellschaft; Ludwigshafen, W. Germany.

TITLE OF REPORT: Report on the in vitro cytogenetic investigations in human lymphocytes with Registration No. 150 732.

AUTHOR(S): Engelhardt, G.

STUDY NUMBER(S): 86/0371.

REPORT ISSUED: November 25, 1986.

CONCLUSION(S) - EXECUTIVE SUMMARY:

Five nonactivated (125, 250, 500, 1000, and 1500 µg/mL) and five S9-activated (250, 500, 1000, 2000, and 2500 µg/mL) doses of test material, Reg. No. 150 732, were evaluated for cytogenetic effects in cultured human lymphocytes. Metaphases were not scored at the highest nonactivated and S9-activated doses owing to cytotoxicity. The mitotic index for cultures exposed to 500 and 1000 µg/mL-S9 and 2000 µg/mL+S9 were markedly reduced compared to the solvent control group. Significant increases in the percentage of cells with aberrations were seen in the 1000-µg/mL nonactivated ($p < 0.01$) and in the 2000-µg/mL S9-activated ($p < 0.05$) dose groups but not at the other treatment levels. The study author concluded that cytotoxicity may be the cause for the chromosome-damaging effects of the test material. We assess that the severe depression in the mitotic indices under both nonactivated and S9-activated conditions may have been associated with the pH of Reg. No. 150 732. Findings from an unscheduled DNA repair assay with Reg. No. 150 732 indicated that doses ≥253 µg/mL caused an acidic change in the pH of the culture medium (see study No. 86/0135). However, there was no indication that the pH of the test material was measured in the human lymphocyte assay. Without this data, we are unable to determine if the clastogenic response is valid or resulted from a treatment condition (i.e., low pH); see Reviewers' Discussion and Interpretation of Study Results, Section D. We assess, therefore, that the study is inconclusive and should be repeated.

Classification: The study in unacceptable; the lack of definitive results indicates that the study should be repeated. It is recommended that the repeat assay be performed with new donor cells, preferably with replicate cultures from different donors or separate experiments with lymphocytes from different donors. Additionally, the repeat assay should include appropriate pH measurements and adjustments, if necessary, to maintain pH levels around neutral during treatment.

A. MATERIALS:

1. Test Material:

Name:	Reg. No. 150 732
Description:	White crystals
Batch No.:	N 32
Purity:	96.5%
Contaminants:	None listed
Solvent used:	Dimethylsulfoxide (DMSO)
Other comments:	The test material was stored at 4°C. The homogeneity and stability of the test material in DMSO were determined analytically.

2. Cell Line: Whole human venous blood was obtained from an unspecified source; 0.5 mL was added to 6 mL of RPMI 1640 tissue culture medium containing 6 µL/mL phytohemagglutinin, and the mixture was incubated for 48 hours at 37°C.

3. S9 Fraction: The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with Aroclor 1254. The S9 reaction mixture contained one volume of the S9 fraction and one volume of the S9-cofactor mix.

4. Positive Controls: Mitomycin C (MMC) at 0.5 µg/mL was used as the nonactivated positive control, and cyclophosphamide (CP) at 6 µg/mL was used as the S9-activated positive control.

B. TEST PERFORMANCE:

1. Preliminary Cytotoxicity Assay: The report indicated that a wide range of test material doses were analyzed in a preliminary cytotoxicity assay. No details were provided.

2. Cytogenetic Assay:

a. Treatment: Duplicate cultures were exposed to five nonactivated (125, 250, 500, 1000, and 1500 µg/mL) and five S9-activated (250, 500, 1000, 2000, and 2500 µg/mL) test material doses, the solvent (DMSO), or the positive controls (0.5 µg/mL MMC-S9 or 6 µg/mL CP+S9). In the nonactivated system, cells were exposed to the selected test material doses, solvent, or positive control for 24 hours.

In the presence of S9 activation, cells were exposed to the test material or controls for 2 hours, washed, refed fresh medium, and incubated for 22 hours. Colcemid (1.33 µg/mL) was added to all cultures in the nonactivated and S9-activated assays 2 to 3 hours prior to cell harvest.

After incubation, metaphase cells were collected, treated with a hypotonic solution, and fixed in methanol:glacial acetic acid (4:1); slides were prepared, stained with 5% Giemsa, and coded.

b. Metaphase Analysis: A maximum of 100 metaphases/culture from the test material dose groups and the negative and solvent controls were scored for structural and numerical chromosome aberrations. Fifty cells per positive control culture were similarly scored. The data were analyzed with and

without gaps. The mitotic index was determined by counting 1500 cells from at least the two highest test doses yielding metaphase cells and for the negative, solvent, and positive control cultures.

c. Statistical Methods: The data were evaluated at p values of 0.05 and 0.01 by Fisher's test.

d. Evaluation Criteria: No criteria to establish the validity of the assay or the biological significance of the results were provided.

C. REPORTED RESULTS:

1. Preliminary Cytotoxicity Assay: The study author stated that "the concentrations which suppressed the mitotic activity by approximately 50% to 60% were 1000 µg/mL (without S9 mix) and 2000 µg/mL (with S9 mix)." Based on these findings, the study author selected 125, 250, 500, 1000, and 1500 µg/mL for the nonactivated assay and 250, 500, 1000, 2000, and 2500 µg/mL for the S9-activated assay.

2. Cytogenetic Assay: As shown in Table 1, mitotic indices were severely suppressed in cultures exposed to 500 and 1000 µg/mL-S9 and 2000 µg/mL+S9 compared to the solvent control cultures; metaphases were not scored from higher dose groups. The cytotoxicity of nonactivated 1000 µg/mL and S9-activated 2000 µg/mL was confirmed in a repeat mitotic index determination. Chromosome aberrations were scored from cultures exposed to three nonactivated (250, 500, and 1000 µg/mL) and three S9-activated (500, 1000, and 2000 µg/mL) doses of the test material. As further shown in Table 1, significant increases in the percentage of cells with aberrations were observed in the 1000 µg/mL nonactivated ($p < 0.01$) and the 2000-µg/mL S9-activated ($p < 0.05$) dose groups. Below these levels, aberration frequencies were generally comparable to the solvent control values. There were no appreciable differences in the number of numerical aberrations among test and negative control groups.

3. Chemical Analysis of Test Material Concentrations: Analytical data presented for test material solutions (250, 500, 1000, and 2000 µg/mL) prepared in DMSO indicated that actual concentrations used in the assay were within 10% of the theoretical values.

TABLE 1. Representative Results of the Human Lymphocyte *in vitro* Cytogenetic Assay with Test Material Registration Number 150 732

Substance	Dose (µg/mL)	S9 Activation	Mitotic Index[a]	No. of Cells Scored	Total[b] No. of Aberrations	% Cells[b] with Aberrations	Biologically[c] Significant Aberrations No./Type
Negative Control							
Culture Medium	--	-	6.56	200	1	0.5	1TB
	--	+	7.23	200	2	1.0	1TB; 1SB
Solvent Control							
Dimethylsulfoxide	--	-	4.30	200	2	1.0	1SF; 1E
	--	+	5.66	200	1	0.5	1TF
Positive Control							
Mitomycin C	0.5	-	1.60	100	>66	58.0**	26E; 5MA
Cyclophosphamide	6.0	+	6.30	100	[d]	19.0**	4E[d]
Test Material							
Reg. No. 150 732	250	-	3.46	200	3	1.5	2SB; 1SF
	500	-	2.06	200	4	1.5	1TB; 3SB
	1000	-	1.26	200	18	9.0**	8TB; 9SB; 1TF
	500	+	9.33	200	2	1.0	1SF; 1E
	1000	+	6.33	200	3	1.5	2TB; 1TF
	2000	+	2.93	200	>13	4.0*	4TB; 4E; 1MA

[a]Based on the count of 1500 cells per culture.
[b]Gaps excluded.
[c]Abbreviations used:
TB - Chromatid break TF - Chromatid fragment E - Exchange
SB - Chromosome break SF - Chromosome fragment MA - Multiple aberrations (≥5 aberrations)
[d]Not all aberrations were reported.
*Significantly different than the solvent control ($p < 0.05$) by Fisher's test.
**Significantly different than the solvent control ($p < 0.01$) by Fisher's test.

The study author concluded that while significant increases were observed at the highest scored nonactivated and S9-activated levels, "cytotoxicity and low solubility of the test substance, might be the cause for the chromosome-damaging (clastogenic) effects in vitro using human lymphocytes."

D. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

We assess, in general agreement with the study author, that no definitive conclusions can be reached regarding the potential clastogenic activity of the test material, Reg. No. 150 732. The study author stated that the test material induced "a dose-dependent, statistically significant increase in the number of aberrant metaphases including and excluding gaps both with and without metabolic activation." The results indicated, however, that positive responses occurred at single doses under nonactivated (1000 µg/mL) and S9-activated (2000 µg/mL) conditions with inconclusive data on a dose response.

The study author attributed the significant clastogenic effects to "special culture conditions, i.e., cytotoxicity and low solubility of the test material." We do not consider test material insolubility to be a valid explanation for the significant effect seen at the highest nonactivated and S9-activated dose levels. It was noted, however, during the review of an unscheduled DNA synthesis assay with Reg. No. 150 732 that concentrations ≥253 µg/mL, prepared in DMSO caused an acidic change in the pH of the culture medium (see DER No. 247-I, Report on the Evaluation of Registration Number 150 732 (ZNT No. 84/150) in the in vitro rat primary hepatocyte unscheduled DNA assay, dated June 1986). Low pH could be responsible for the significant clastogenic effect observed in the human lymphocytes. Brusick[1] demonstrated that during treatment, reduced pH conditions can induce cytotoxic effects and marked increases in chromosome aberrations in mammalian cells. It is possible, therefore, that a pH change affected the mitotic index and caused the increased frequency of aberrations.

The currently reviewed study provided no information indicating that the pH of the treatment medium was measured or adjusted to maintain a neutral pH. We are, therefore unable to assess the impact, if any, of the test material at

[1]Brusick, D. Genotoxic effects in cultured mammalian cells produced by low pH treatment conditions and increased ion concentrations. Environ. Mutagenesis (1986) 8(6): 879-886.

on the outcome of the study. It was noteworthy, however, that significant clastogenic activity occurred at doses that severely reduced the mitotic index (1000 µg/mL-S9 and 2000 µg/mL+S9).

We conclude, therefore, that the assay should be repeated and steps should be taken to minimize possible pH effects on treatment conditions. We further recommend that the repeat assay be performed with new donor cells, preferably with replicate cultures from different donors or separated experiments with lymphocytes from different donors. The investigators should also adopt the more conventional method for scoring cells with multiple aberrations (i.e., cells with ≥10 aberrations are considered to be multiple aberrations).

E. QUALITY ASSURANCE MEASURES: A quality assurance statement was signed and dated November 25, 1986.

F. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 0011-0022.

APPENDIX A

Methods and Materials
(p. 0011-0022)

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EPA No.: 68D80056
DYNAMAC No.: 247-G
TASK No.: 2-47G
December 7, 1989

[illegible] FORMATION
[illegible] ON (SO 12065)

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--In vivo Cytogenetic Assay with Chinese Hamsters

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Robert J. Weir

Date: 12-5-89

228

EPA No.: 68D80056
DYNAMAC No.: 247-G
TASK No.: 2-47G
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--*In vivo* Cytogenetic Assay with Chinese Hamsters

REVIEWED BY:

Nancy E. McCarroll, B.S.
Principal Reviewer
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Signature: Nancy E. McCarroll
Date: 12-7-89

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Date: 12/12/89

Marion Copley, D.V.M.
D.A.B.T.
Review Section II
EPA Section Head, Section II
Toxicology Branch I
(H-7509C)
Signature: Marion Copley
Date: 1/2/90

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DATA EVALUATION RECORD

CHEMICAL: Quinclorac.

STUDY TYPE: Mutagenicity--In vivo cytogenetic assay with Chinese hamsters.

ACCESSION/MRID NUMBER: 410635-30.

TEST MATERIAL: Registration No. 150 732.

SYNONYM: 3,7-Dichloro-8-quinolinecarboxylic acid; BAS 514 H.

SPONSOR: BASF Corporation Chemical Division, Parsippany, NJ.

TESTING FACILITY: BASF Aktiengesellschaft, Ludwigshafen, W. Germany.

TITLE OF REPORT: Report on the cytogenetic study in vivo of Reg. No. 150 732 in Chinese Hamsters; bone marrow chromosome analysis: single oral administration.

AUTHOR: Engelhardt, G.

STUDY NUMBER: 88/1086.

REPORT ISSUED: June 13, 1988.

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CONCLUSIONS/EXECUTIVE SUMMARY:

The potential of test material, Reg. No. 150 732 to induce chromosome damage was investigated in Chinese hamsters. Groups of 10 animals (5 males and 5 females) received single oral gavage administrations of 2000 or 4000 mg/kg of the test material and were sacrificed 24 hours postexposure. Thirty animals were subdivided into groups of 10 (5 males and 5 females), dosed with 8000 mg/kg, and sequentially sacrificed 6, 24, and 48 hours following treatment. Signs of irregular respiration, apathy, and generally poor condition were seen in all dose groups. A significant increase in the percentage of cells with aberrations was observed in the high-dose animals at the 24-hour harvest but at no other sampling interval; the effect was neither dose nor time dependent. Since a high frequency of aberrations occurred in the negative control group (males only) and there was an unusually high incidence of "marker chromosomes" in 6 of the 70 animals used in this study, the experiment was repeated using animals from a different commercial source.

The results of the repeat assay, conducted with 8000 mg/kg of the test material, did not confirm the earlier findings. No significant increases in chromosome aberrations were seen in the bone marrow cells of male and female Chinese hamsters harvested 6, 24, or 48 hours postexposure to 8000 mg/kg.

We conclude, therefore, that since the initial significant response was not time or dose related and was not reproduced in the repeat assay, the test material, Reg. No. 150 732, was not clastogenic in this in vivo cytogenetic assay.

Study Classification: The study is acceptable.

A. MATERIALS:

1. Test Material:

Name:	Reg. No. 150 732
Description:	White crystals
Batch No.:	N57
Purity:	98.3%
Contaminants:	None listed
Solvent used:	0.5% aqueous carboxymethylcellulose (CMC).
Other comments:	The test material was stored at 4°C. The homogeneity and stability of a comparable batch of the test material (not identified) prepared in water was determined analytically. Suspensions of the test material used in the analysis were prepared immediately prior to use.

2. Test Animals:

a. Source:

- Initial Study: Adult male and female Chinese hamsters (7 to 13 weeks of age) having a mean weight of ≈25 g were obtained from Hoffman-LaRoche, Fullinsdorf, SZ.

- Repeat Study: Adult male and female Chinese hamsters (7 to 13 weeks of age) having a mean weight of ≈30g were obtained from Knoll AG, Ludwigshafen, W. Germany.

b. Animal Maintenance: Animals were housed in groups of five during the conditioning period and individually thereafter, under environmental conditions controlled for temperature (20-24°C), relative humidity (30-70%), and light (12 hours/day). Standard feed (Kliba Haltungsdiat) and drinking water were available ad libitum.

c. Assignment to Groups: Animals were identified by card number, randomized, and assigned to the following test groups:

Test Group	Dose	Males Group	Females Group	Sacrifice Interval
Initial Study				
Vehicle Control				
0.5% Carboxymethylcellulose (CMC)	10 mL	5	5	24
Positive Control				
Cyclophosphamide (CP)	40 mg/kg	5	5	24
Test Material				
High dose	8000 mg/kg	5	5	6
		5	5	24
		5	5	48

Test Group	Dose	Males/ Group	Females/ Group	Sacrifice Interval Hours)
Mid dose	4000 mg/kg	5	5	[illegible]
Low dose	2000 mg/kg	5	5	[illegible]
Repeat Study[a]				
Vehicle Control				
0.5% CMC	20 mL	5	5	[illegible]
Positive Control				
CP	40 mg/kg	5	5	[illegible]
Test Material				
High dose	8000 mg/kg	5	5	[illegible]
		5	5	[illegible]
		5	5	[illegible]

[a]The dose(s) of the test material, vehicle, and positive control were administered once by oral gavage.

B. STUDY DESIGN:

1. Preliminary Toxicity Study: An acute oral toxicity study was performed; the details were not reported. The author stated, however, that one animal receiving 10,000 mg/kg of the test material died, and clinical signs of toxicity (irregular respiration, apathy, and generally poor condition) were seen in animals administered 8250 mg/kg of the test material. The study author, therefore, selected 2000, 4000, and 8000 mg/kg as the low, intermediate, and high dose, respectively, for the cytogenetic assay.

2. Cytogenetic Study:

a. Initial Study:

1. Compound Administration: Thirty animals (15 males and 15 females) were administered a single oral gavage dose of 8000 mg/kg. The mid- and low-test material doses as well as the vehicle (0.5% CMC) and positive (40 mg/kg CP) control compounds were similarly administered once by oral gavage; each

of these groups consisted of five male and five female Chinese hamsters. All animals were observed for clinical signs of toxicity.

2. Animal Sacrifice: Representative males and females in the high-dose group were sacrificed by an unspecified method at 6, 24, and 48 hours post-exposure to 8000 mg/kg of the test material. Animals in the mid- and low-test material dose groups and the vehicle and positive control groups were sacrificed 24 hours following treatment. All animals received a single intraperitoneal injection of 3.3 mg/kg colcemid ~2 hours prior to the scheduled sacrifice.

3. Bone Marrow Harvest: Bone marrow cells were collected from both femurs by aspiration into Hanks' solution. Cells were centrifuged, treated with hypotonic 1% sodium citrate, and fixed in methanol:glacial acetic acid (3:1). Slides were stained with 5% Giemsa and coded.

4. Slide Analysis: A maximum of 100 metaphases per animal were scored for the presence of structural and numerical aberrations. Gaps were counted and data were evaluated with and without gaps.

5. Statistical Evaluation: The data were analyzed for statistical significance at p values of 0.05 and 0.01 by Fisher's Exact test and the Mann-Whitney U test.

6. Repeat Study: The repeat cytogenetic assay was conducted as described for the initial assay with the exception that the low- and mid-test material dose groups were not included. The animals used in the repeat study were obtained from a different commercial source because of the unusually high incidence of "marker chromosomes" observed in the animals from the initial assay.

C. REPORTED RESULTS:

1. Test Material Analyses: Data presented by the study author from the analysis of test material solutions indicated that in both the initial and repeat assays, the actual concentrations of test material, Reg. No. 150 732, were within 10% of the nominal concentrations. Values from duplicate

samples analyzed for achieved concentrations were generally comparable, indicating that the test material was uniformly distributed throughout the dosing solutions.

2. Animal Observations: No animals died while on study. Clinical signs of irregular respiration were noted in all dose groups within 30 minutes of test material administration. Approximately 2 to 3 hours postexposure, apathy and a generally poor condition were observed in all dose groups. The report indicated that some of these signs persisted until the scheduled sacrifice.

3. Cytogenetic Assay

   a. Initial Test: Representative results from the initial assay are presented in Table 1. As shown, analysis of metaphases recovered from high-dose males and females 24 hours posttreatment revealed an increase in the percentage of cells with aberrations; the combined data for both sexes were significantly ($p < 0.05$) different than the combined vehicle control group value. No significant effects were observed in the high-dose group at the 6- or 48-hour harvest interval or in the low- and mid-dose groups harvested 24 hours postexposure. The frequency of numerical aberrations in treatment groups was generally comparable to the vehicle control group values. The study author stated that the significantly increased percentage of aberrant cells in the 8000-mg/kg (24-hour harvest) dose group was "influenced by only a few animals (less than 50% of the animals/group) and that more than 50% of the hamsters have an aberration rate in the range of that of the control." The study author further stated that both the relatively high frequency of aberrations in the negative control group and the unusually high frequency of "marker chromosomes" in 6 of the 70 hamsters suggested that the animals used in this study were probably of "poor quality." Our reviewers noted a relatively high frequency of cells with multiple aberrations in both the control and test groups. Although the occurrence of multiple aberrations is expected in the positive control group, they are rarely seen in untreated animals.

Based on the unusual findings of this study, a repeat assay was performed with Chinese hamsters obtained from a different commercial source.

TABLE 1. Representative Results of the Initial *in vivo* Cytogenetic Assay in Chinese Hamsters Exposed to Test Material, Reg. No. 150 732

Substance	Dose	Exposure Time (hrs.)	Sex	No. of Animals Examined per Group	No. of Metaphases Examined	Total Number of Cells with Aberrations[a]	% Cells with Abberations[a]	% Cells with with >1 Aberrations per Group[b]	Total No. of Aberrations per Cell[b]	No. of Aberrations per Cell[b]	Biologically significant Aberrations No./Type[c]
Vehicle Control											
0.5% Carboxy-methylcellulose	20 mL	24	M	5	500	8	1.6 (0.8)[d]	0.4	≥24	>0.02	3TB; 1SB; 4M
			F	5	500	0	0.0				
Positive Control											
Cyclophosphamide	40 mg/kg	24	M	5	500	165	33.0 (36.8)**	12.9	≥846	>0.85	129M; 13SE; 6SP
			F	5	500	203	40.6				
Test Material											
Reg. No. 150 732	2000 mg/kg	24	M	5	500	4	0.8 (1.0)	0.5	>22	>0.02	1STB; 3SB; 1SF; 1M
			F	5	500	6	1.2				
	4000 mg/kg	24	M	5	500	8	1.6 (0.9)	0.4	>23	>0.02	9TB; 3SB; 2M; 1E
			F	5	500	1	0.2				
	8000 mg/kg	6	M	5	500	2	0.4 (0.2)	0.1	≥ 6	>0.01	1TB; 1M
			F	5	500	0	0.0				
		24	M	5	500	11	2.2 (1.9)*	1.3	≥62	>0.06	1STB; 4SB; 2TF; 8M; 1E
			F	5	500	8	1.6				
		48	M	5	500	3	0.6 (0.6)	0.2	10	0.01	7TB; 1SB; 1TF; 1SF
			F	5	500	3	0.6				

[a]Gaps excluded.

[b]Results tabulated by our reviewers.

[c]Abbreviations used to identify type and frequency of aberrations combined for both sexes and tabulated by our reviewers.

TB - Chromatid break
SB - Chromosome break
E - Exchange
TF - Chromatid fragment
SF - Chromosome fragment
P - Pulverized Cell
M - Multiple aberrations (≥5 aberrations/cell)

[d]Values in ( ) = combined results for males and females.

*Significantly different from the control ($p < 0.05$) by Fisher's Exact or Mann Whitney U test.
**Significantly different from the control ($p < 0.01$) by Fisher's Exact or Mann Whitney U test.

b. Repeat Test: The repeat assay was performed as described for the initial test; however, only the high dose of the test material (8000 mg/kg), the vehicle (0.5 CMC), and the positive (40 mg CP/kg) control were included. Groups of 10 animals (5 males and 5 females) administered 8000 mg/kg of the test material were sacrificed 6, 24, and 48 hours following treatment. All control animals were sacrificed at 24 hours. Results showed no significant increases in the percentage of cells with aberrations in the three groups of male and female hamsters receiving the high dose of Reg. No. 150 732 (Table 2).

The study author concluded, "Thus, according to these results the test substance Reg. No. 150 732 is considered not to have any chromosome-damaging (clastogenic) effect under the experimental conditions chosen here."

D. REVIEWERS' DISCUSSION/INTERPRETATION OF RESULTS:

We agree with the study author's conclusion that test material, Reg. No. 150 732 was not clastogenic in this in vivo cytogenetic assay for the following reasons:

1. The significant effect observed in the high-dose group (24-hour harvest only) of the initial assay was not dose or time dependent.

2. The effect was not reproducible.

We do, however, question the classification of ≥5 aberrations per cell as a multiple aberration. By convention, only cells with ≥10 aberrations per cell are assigned to this group of aberrations. Nevertheless, we do not feel that this deviation from recognized scoring schemes altered the outcome of the study. Although one multiple aberration was scored in the 24-hour harvest group exposed to 8000 mg/kg of the test material in the repeat assay, the occurrence of this aberration in 1 of 10 animals and in 1 of 1000 cells does not constitute sufficient evidence of a clastogenic effect. We conclude, therefore, that the initial results were anomalous and that the negative findings of the repeat assay are valid.

E. QUALITY ASSURANCE MEASURES: A quality assurance statement was signed and dated June 13, 1988.

F. CBI APPENDIX: Appendix A, Material and Methods, CBI pp. 0015-0028.

TABLE 2. Representative Results of the Repeat *in vivo* Cytogenetic Assay in Chinese Hamsters Exposed to Test Material, Reg. No. 150 732

Substance	Dose	Exposure Time (hrs.)	Sex	No. of Animals Examined per Group	No. of Metaphases Examined	Total Number of Cells with Aberrations[a]	% Cells with Aberations[a]	% Cells with with >1 Aberrations per Group[b]	Total No. of Aberrations per Cell[b]	No. of Aberrations per Cell[b]	Biologically Significant Aberrations No./Type[c]
Vehicle Control											
0.5% Carboxy-methyl cellulose	20 mL	24	M	5	500	1	0.2 (0.1)[d]	0.1	2	0.002	2TB
			F	5	500	0	0.0				
Positive Control											
Cyclophosphamide	40 mg/kg	24	M	5	500	140	28.0 (51.8)*	11.1	>734	>0.734	111M; 144E; 35P
			F	5	500	178	35.6				
Test Material											
Reg. No. 150 732	8000 mg/kg	6	M	5	500	2	0.4 (0.7)	0	6	0.006	5TB; 1SB
			F	5	400[e]	4	1.0				
		24	M	5	500	1	0.2 (0.1)	0	1	0.001	1TB
			F	5	500	0	0.0				
		48	M	5	500	0	0.0 (0.1)	0.1	>5	0.005	1M
			F	5	500	1	0.2				

[a]Gaps excluded.

[b]Results tabulated by our reviewers.

[c]Abbreviations used to identify type and frequency of aberrations data combined for both sexes and tabulated by our reviewers.

TB - Chromatid break
SB - Chromosome break
E - Exchange
TF - Chromatid fragment
SF - Chromosome fragment
P - Pulverized Cell
M - Multiple aberrations (≥5 aberrations/cell)

[d]Values in ( ) = combined results for males and females.

[e]Metaphases from one female were not scored; the reason was not specified.

*Significantly different from the control ($p < 0.01$) by Fisher's Exact or Mann Whitney U test.

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APPENDIX A

Materials and Methods
CBI pp. 0016-0028.

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Pages 240 through 252 are not included.

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____ The product confidential statement of formula.

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EPA No.: 68D80056
DYNAMAC No.: 247-C
TASK No.: 2-47C
December 7, 1989

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DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Microbial Mutagenicity Assays with
Salmonella typhimurium and Escherichia coli

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: [signature]

Date: 12/5/89

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EPA No.: 68D80056
DYNAMAC No.: 247-C
TASK No.: 2-47C
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Microbial Mutagenicity Assays with *Salmonella typhimurium* and *Escherichia coli*

REVIEWED BY:

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EPA Section Head,
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(H-7509C)
Signature: Marion Copley
1/2/90

DATA EVALUATION RECORD

CHEMICAL: Quinclorac.

STUDY TYPE: Mutagenicity--Microbial mutagenicity assays with Salmonella typhimurium and Escherichia coli.

MRID/ACCESSION No.: 410635-28.

TEST MATERIAL: Registration No. 150 732.

SYNONYMS/CAS No.: 3,7-Dichloro-8-quinolinecarboxylic acid; BAS 514 H.

SPONSOR: BASF Corporation Chemical Division, Parsippany, NJ.

TESTING FACILITY: BASF Aktiengesellschaft, Ludwigshafen, W. Germany.

TITLE OF REPORT: Report on the Study of Registration Number 150 732 in the Ames Salmonella/Mammalian Microsome Mutagenicity Test and Reverse Mutation Assay--E. coli WP2 uvrA (Standard Plate Test and Preincubation Test). Dated August 30, 1988.

AUTHOR(S): Engelhardt, G.

STUDY No(s).: 88/0358.

REPORT ISSUED: August 18, 1988.

CONCLUSION(S)/EXECUTIVE SUMMARY: Five doses of test material Registration (Reg.) No. 150 732 ranging from 20 to 5000 ug/plate failed to induce a cytotoxic or mutagenic effect in Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 or in Escherichia coli strain WP2 uvrA under nonactivated or S9-activated conditions in either a standard plate incorporation or a 20-minute preincubation assay. In the absence of test-material insolubility or cytotoxicity, 5000 µg/plate is considered to be an acceptable high dose for microbial mutagenicity assays. However, the S9-activated assays were conducted with an excessive concentration of S9 liver homogenates in the S9 mix (30%). Unless the author can justify the use of a high liver enzyme level, the study should be repeated using the recommended screening concentration of S9 (4% S9 in the S9 cofactor mix).[1] Additionally, the results of the chemical analysis on test material solutions prepared for these assays were not reported.

Study Classification: The study is unacceptable.

A. MATERIALS:

1. Test Material:

Name:	Reg. No. 150 732
Description:	White crystals
Batch No.:	III/2 N57
Purity:	98.29%
Contaminants:	None listed
Solvent used:	Dimethylsulfoxide (DMSO)
Other comments:	The test material was stored at 4°C. The homogeneity and stability of the test material in DMSO was determined analytically; the results of these analyses were not presented.

2. Control Materials:
Negative: DMSO
Solvent/final concentration: 100 µg/plate
Positive: Nonactivation:

N-Methyl-N'-nitro-N-nitrosoguanidine	5 µg/plate	TA100, TA1535
4-Nitro-o-phenylenediamine	10 µg/plate	TA98
9-Aminoacridine	100 µg/plate	TA1537
N-Ethyl-N'-nitro-N-nitrosoguanidine	10 µg/plate	E. coli WP2 (uvrA)

[1]Maron, M., and Ames, B.N. Revised methods for the Salmonella mutagenicity test. Mutat. Res. 113 (1983): 173-215.

Activation:
2-Aminoanthracene (2AA) 10 µg/plate all S. typhimurium strains.

2-Aminoanthracene (2-Anthramine) 60 µg/plate
E. coli WP2 uvrA.

3. Activation: S9 derived from

x	Aroclor 1254	x	induced	x	rat	x	liver
	phenobarbital		noninduced		mouse		lung
	none				hamster		other
	other				other		

If other, describe below. Describe S9 composition (if purchased, give details). The S9 mix contained 30% S9 liver homogenate.

4. Test Organism Used: S. typhimurium strains

	TA97	x	TA98	x	TA100		TA102		TA104
x	TA1535	x	TA1537		TA1538; list any others:				

E. coli WP2 uvrA.

Test organisms were properly maintained: YES.
Checked for appropriate genetic markers (rfa mutation, R factor): YES.

5. Test Compound Concentrations Used:

Nonactivated conditions: 20, 100, 500, 2500, and 5000 µg/plate.

Activated conditions: As above.

B. TEST PERFORMANCE:

1. Type of Salmonella Assay: x Standard plate test
   x Pre-incubation (20) minutes
   ____ "Prival" modification
   ____ Spot test
   ____ Other (describe).

2. Preliminary Cytotoxicity Assay: A preliminary cytotoxicity assay was not performed.

3. Mutagenicity Assay: Five doses of the test material ranging from 20 to 5000 µg/plate were tested in the nonactivated and S9-activated plate incorporation and preincubation mutation assays. Representative results of the plate incorporation and preincubation assays are presented in Tables 1 and 2, respectively. As shown, the

test material was neither cytotoxic nor mutagenic in S. typhimurium TA1535, TA1537, TA98, or TA100 or in E. coli WP2 uvrA either with or without S9 activation. Although slight decreases in tryptophan-revertant colonies of E. coli WP2 uvrA were noted at the highest assayed dose (5000 µg/plate) both with and without S9 activation and in both the plate incorporation and preincubation assays, these reductions were not considered definitive evidence of a cytotoxic effect. By contrast to the uniformly negative test material results, all strains responded to the mutagenic action of the appropriate nonactivated positive controls in both assays. Similarly, all strains responded to S9-activated 2AA; however, the doses of 2AA (10 µg/plate for all S. typhimurium strains and 60 µg/plate for E. coli) that were used and the concentration of S9 in the S9 mix (30%) were excessive.

Based on the combined results of both assays, the study author concluded, "According to the results of the present study, the test substance Reg. No. 150 732 is not mutagenic in the Ames test and Escherichia coli reverse mutation assay under the experimental conditions chosen here."

4. Reviewers' Discussion/Conclusions: We assess that the test material, Reg. No. 150 732, was assayed up to an acceptably high dose (5000 µg/plate) for nonprecipitating and noncytotoxic compounds with no evidence of a mutagenic effect. However, the use of 30% S9 as the primary screening concentration is not recommended[2] and may have compromised the sensitivity of the system to detect a potential promutagen that may be deactivated by high enzyme levels.

Although conversion of the promutagen 2AA to an active mutagenic metabolite was demonstrated, the doses of 2AA (10 µg/plate for all S. typhimurium strains and 60 µg/plate for E. coli) were higher than what is conventionally applied in this test system. Using the recommended concentration of S9 in the S9 mix (4%), peak mutagenic activity of 2AA can be detected by S. typhimurium strains at doses ranging from 0.5 to 2.5 µg/plate and peak detection by E. coli WP2 uvrA can be achieved at ≈ 10 µg/plate. It is not clear whether these high levels of 2AA were required because of the excessive amount of S9 in the activation mix.

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[2]Ibid.

TABLE 1. Representative Results of the Plate Incorporation Microbial Mutagenicity Assay with Reg. No. 150 732

Substance	S9 Activation	Dose plate (µg/plate)	Revertants per Plate of Bacterial Tester Strain[a]				
			S. typhimurium				E. coli
			TA1535	TA1537	TA98	TA100	WP2uvrA
Negative Control							
Dimethylsulfoxide	-	--	19 ± 3	11 ± 2	24 ± 3	136 ± 7	33 ± 5
	+	--	20 ± 4	14 ± 1	38 ± 4	134 ± 4	44 ± 3
Positive Controls[b]							
MNNG	-	5	2187 ± 300	--	--	2133 ± 126	--
4NPA	-	10	--	--	855 ± 54	--	--
9AA	-	100	--	717 ± 29	--	--	--
ENNG	-	10	--	--	--	--	827 ± 51
2AA	+	10	445 ± 41	134 ± 33	1300 ± 10	1653 ± 165	--
	+	60	--	--	--	--	770 ± 13
Test Material							
	-	5000[c]	20 ± 3	12 ± 2	30 ± 1	115 ± 13	39 ± 3
Reg. no. 150 732	+	5000	18 ± 3	10 ± 2	30 ± 2	111 ± 8	28 ± 5

[a] Means and standard deviations of counts from triplicate plates.

[b] Abbreviations used:
MNNG - N-methyl-N'-nitro-N-nitrosoguanidine
4NPA - 4-nitro-o-phenylenediamine
9AA - 9-Aminoacridine
ENNG - N-ethyl-N'-nitro-N-nitrosoguanidine
2AA - 2-Aminoanthracene.

[c] Results for lower doses (20, 100, 500, and 2500 µg/plate/+ or -S9) were comparable to the appropriate control values.

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TABLE 2. Representative Results of the Preincubation Microbial Mutagenicity Assay with Reg. No. 150 732

Substance	S9 Activation	Dose plate (µg/plate)	Revertants per Plate of Bacterial Tester Strain[a] S. typhimurium TA1535	TA1537	TA98	TA100	E. coli WP2uvrA
Solvent Control							
Dimethylsulfoxide	-		22 ± 3	8 ± 1	21 ± 3	114 ± 3	11 ±
	+		19 ± 3	8 ± 1	33 ± 3	120 ± 13	21 ±
Positive Controls[b]							
MNNG		5	810 ± 22	--	--	1040 ± 12	
4NPA	-	10	--	--	710 ± 37	--	
2AA	-	100	--	545 ± 64	--		
ENNG	-	10	--	--	--	--	1265 ±
2AA	+	10	282 ± 26	127 ± 12	883 ± 68	1520 ± 51	
	+	50	--	--	--	--	721 ±
Test Material							
Reg. No. 150 732		5000[c]	13 ± 1	8 ± 3	19 ± 3	116 ± 12	1
	+	5000	17 ± 5	8 ± 2	26 ± 3	120 ± 9	8 ±

[a] Means and standard deviations of counts from triplicate plates

[b] Abbreviations used:
MNNG N-methyl-N'-nitro-N-nitrosoguanidine
4NPA 4-nitro-o-phenylenediamine
2AA 2-Aminoacridine
ENNG N-ethyl-N'-nitro-N-nitrosoguanidine
2AA 2-Aminoanthracene.

[c] Results for lower doses (20, 100, 500, and 2500 µg plate + ... were comparable to the appropriate control values.

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We conclude, therefore, that unless the biochemical characteristics of the test material indicate a requirement for high enzyme levels, the use of 30% S9 as the primary screening concentration is not an acceptable practice.

5. Quality Assurance: A quality assurance statement was signed and dated August 30, 1988.

6. CBI Appendix: Appendix A, Materials and Methods, CBI pp. 0011-0020.

APPENDIX A

Materials and Methods
CBI pp. 0011-0020

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EPA No.: 38D80056
DYNAMAC No.: 247-H
TASK No.: 2-47H
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Mouse Micronucleus Assay

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: _____

Date: _____

EPA No.: 68D80056
DYNAMAC No.: 247-H
TASK No.: 2-471I
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Mouse Micronucleus Assay

REVIEWED BY:

Nancy E. McCarroll, B.S.
Principal Reviewer
Dynamac Corporation
Signature: Nancy E. McCarroll
Date: 12-7-89

I. Cecil Felkner, Ph.D.
Independent Reviewer
Dynamac Corporation
Signature:
Date:

APPROVED BY:

Roman Pienta, Ph.D.
Department Manager
Dynamac Corporation
Signature:
Date:

William Greear, M.P.H.
EPA Reviewer, Section II
Toxicology Branch I
(H-7509C)
Signature:
Date: 12/11/89

Marion Copley, D.V.M., D.A.B.T.
Review Section II
EPA Section Head,
Toxicology Branch I
(H-7509C)
Signature:
Date:

DATA EVALUATION RECORD

CHEMICAL: Quinclorac.

STUDY TYPE: Mutagenicity--Mouse micronucleus assay.

MRID/ACCESSION NUMBER: 410635-29.

TEST MATERIAL: Registration No. 150 732.

SYNONYMS/CAS NO. 3,7-Dichloro-8-quinolinecarboxylic acid; BAS 514 H.

SPONSOR: BASF Corporation Chemical Division, Parsippany, NJ.

TESTING FACILITY: BASF Aktiengesellschaft; Ludwigshafen, W. Germany.

TITLE OF REPORT: Report on the cytogenetic investigations in NMRI mice after a single oral administration of Registration No. 150 732 Micronucleus test.

AUTHOR(S): Engelhardt, G.

STUDY NUMBER(S): 86/0018.

REPORT ISSUED: February 3, 1986.

CONCLUSION(S) - EXECUTIVE SUMMARY:

Under the conditions of the study, the single oral administration of 500, 1000, and 2000 mg/kg of test material, Reg. No. 150 732, to male and female mice did not significantly increase the frequency of micronucleated polychromatic erythrocytes (MPEs). Bone marrow cells were harvested 24 hours postexposure to the low and mid doses of the test material and 16, 24, and 48 hours after administration of the high dose. Toxic signs including irregular respiration, apathy, and piloerection were noted in the mid- and high-dose animals indicating that the range of concentrations selected for this assay was adequate. However, the high-dose group did not include a 72-hour postadministration harvest; therefore, the study design was not adequate to assure the formation of micronuclei in the event that the test chemical caused moderate-to-severe mitotic delay.

Study Classification: The study is unacceptable.

A. MATERIALS:

1. Test Material:

Name:	Reg. No. 150 732
Description:	Colorless crystals
Lot No.:	N 32
Purity:	96.5%
Contaminants:	None listed
Solvent used:	0.5% Carboxymethylcellulose (CMC)
Other comments:	The test material was stored at 4°C and was suspended in 0.5% CMC. The homogeneity and stability of the test material in water were determined analytically.

2. Control Materials: None.
Negative/Route of administration:

Vehicle/Final concentration/Route of administration
0.5% CMC was administered once by oral gavage at a dosing volume of 10 mL.

Positive/Final concentration/Route of administration
Cyclophosphamide (CP) at 40 mg/kg was administered once by oral gavage.

3. Test Compound:
Route of administration: Oral gavage
Dose levels used: 500, 1000, and 2000 mg/kg.

4. Test Animals:

a. Species Mouse Strain NMRI Mean weight 27.5 g.
Source: Charles River GmbH, Sulzfeld, W. Germany.

b. No. animals used per dose: (high-dose group): 15 males
15 females
(all other groups): 5 males 5 females.

c. Properly maintained? YES.

B. TEST PERFORMANCE:

1. Treatment and Sampling Times:

a. Test compound
Dosing: X once _____ twice (24 hr apart)
_____ other (describe):

Sampling (after last dose): _____ 6 hr X 16 hr
X 24 hr X 48 hr (high-dose group)

(after last dose): X 24 hr (mid- and low-dose groups and vehicle control group)

b. Positive control
Dosing: X once _____twice (24 hr apart)
_____ other (describe):
Sampling (after last dose): _____ 6 hr _____ 12 hr
X 24 hr _____ 48 hr _____ 72 hr
_____ other (describe):

2. Tissues and Cells Examined:

X bone marrow _____ other (list):
No. of polychromatic erythrocytes (PCE) examined per animal: 1000.
No. of normochromatic erythrocytes (NCE; more mature RBCs):
The number of NCEs was determined per 1000 PCEs/animal.

C. REPORTED RESULTS:

1. Chemical Analyses: Data presented by the study author for the analysis of test material solutions indicated that the actual concentrations of test material Reg. No. 150 732 were 122%, 116%, and 101% of the nominal concentrations, which were 200, 100, and 50 mg/mL, respectively.

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Values for duplicate samples analyzed for achieved concentration were generally comparable, indicating that the test material was uniformly distributed throughout the dosing solutions.

2. Acute Toxicity Test: The report stated that deaths were observed in animals receiving 2610 mg/kg; at a dose of 2150 mg/kg, all animals survived but clinical signs including irregular respiration, piloerection, and apathy were noted 5 hours after exposure. Some of these signs were reported to have persisted for 3 days posttreatment. Based on these findings, the doses selected for the micronucleus assay were 500, 1000, and 2000 mg/kg. Our reviewers noted that the clinical signs observed in mice were similar to those reported in Chinese hamsters receiving oral doses of the test material.[1]

3. Micronucleus Assay:

   a. Animal observations: Although one animal died in the 2000-mg/kg dose group, the author did not attribute this death to test material administration. Clinical signs of irregular respiration, apathy, and piloerection were observed the day following administration of the mid and high test doses. In the low-dose group, "a few" animals exhibited irregular respiration and piloerection. Necropsies of the animals in the treatment groups did not reveal any gross lesions that could be attributed to the single oral administration of Reg. No. 150 732.

   b. Micronucleus assay: Representative results from the micronucleus assay conducted with the test material are presented in Table 1. As shown, the three doses of the test material (500, 1000, or 2000 mg/kg) did not appreciably increase the frequency of MPEs in males and females at the single harvest for the low- and mid-dose groups or at the three sacrifice intervals for the high-dose group. The data combined for both sexes at each experimental point were not significantly different from the control group results. The report indicated that slight inhibition of erythropoiesis was evident in some animals in the 1000-mg/kg dose group and in the 2000-mg/kg dose groups at the 24- and 48-hour sacrifice intervals. The frequency of NCEs per 1000 PCEs in these groups, either by sex or combined for both sexes, were, however, within the normal range expected for this parameter.

   Based on these findings, the study author concluded, "Thus, under the experimental conditions chosen here, the test substance Reg. No. 150 732 does not have any chromosome-damaging (clastogenic) effect, and there were no indications of any impairment of distribution in the course of mitosis."

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[1]Data Evaluation Record 247-G, Report on the cytogenetic study in vivo of Reg. 150 732 in Chinese Hamsters; bone marrow chromosome analysis; single oral administration; study No. 88/0186; dated June 13, 1988.

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TABLE 1. Representative Results of the Micronucleus Assay in Mice with Reg. No. 150 732

Substance	Dose (mg/kg)	Exposure Time[a] (hours)	Sex	No. of Animals Analyzed per Group	No. of PCEs[b] Analyzed per Group	Percent MPEs[c] per Group	MCEs[c] per 1000 PCEs
Negative Control							
0.5% Carboxymethyl-cellulose	--	24	M	5	5000	0.12	0.336
			F	5	5000	0.14	0.344
Positive Control							
Cyclophosphamide	40	24	M	5	5000	2.78[d]	0.377
			F	5	5000	2.12[d]	0.583
Test Material							
Reg. No. 150 732	500	24	M	5	5000	0.14	0.343
			F	5	5000	0.22	0.397
	1000[e]	24	M	5	5000	0.24	0.369
			F	5	5000	0.16	0.758
	2000[e]	16	M	5	5000	0.12	0.458
			F	5	5000	0.10	0.409
		24	M	4[f]	4000	0.25	0.765
			F	5	5000	0.12	0.471
		48	M	5	5000	0.12	0.500
			F	5	5000	0.10	0.364

[a] Time after compound administration.

[b] Abbreviations used:
PCE--Polychromatic erythrocytes
MPE--Micronucleated polychromatic erythrocytes
MCE--Normochromatic erythrocytes.

[c] Calculated by our reviewers.

[d] Reported to be positive by the study author.

[e] Clinical signs of irregular respiration, apathy, and piloerection noted 1 day following compound administration.

[f] One animal died; this death was not considered to be compound related.

D. REVIEWERS' DISCUSSION/CONCLUSIONS:

We assess that the evidence of toxic signs in mid- and high-dose animals indicated that the test material was assayed at an appropriate concentration range. However, the study was flawed by the lack of a 72-hour sampling interval for the high-dose group: sampling at 24, 48, and 72 hours is the recommended approach.[2]

Although the results did not suggest that micronuclei induction in the high-dose group increased with time, sampling 72 hours post-exposure would have provided assurance that the potential for micronucleus formation was optimal in the event of moderate-to-severe mitotic delay.

E. QUALITY ASSURANCE MEASURES: A quality assurance statement was signed and dated February 3, 1986.

F. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 0011-0021.

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[2]Heddle, J. A., Hite, M., Kirkhart, B., Mavourin, K., MacGregor, J. T., Newell, G. W., and Salamone, M. F. The induction of micronuclei as a measure of genotoxicity. A report of the U.S. Environmental Protection Agency Gene-Tox Program, Mutat. Res. 123(1983): 61-118.

APPENDIX A

Materials and Methods
CBI pp. 0011-0021.

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Page_____ is not included in this copy.

Pages 282 through 292 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

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____ The product confidential statement of formula.

____ Information about a pending registration action.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

EPA No.: 68D80056
DYNAMAC No.: 247-J
TASK No.: 2-47J
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Rec Assay with Bacillus subtilis

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: [signature]
Date: 12/6/89

EPA No.: 68D80056
DYNAMAC No.: 247-J
TASK No.: 2-47J
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Rec Assay with Bacillus subtilis

REVIEWED BY:

Nancy E. McCarroll, B.S.
Principal Reviewer
Dynamac Corporation

Signature: Nancy E. McCarroll
Date: 12-7-89

I. Cecil Felkner, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: I. Cecil Felkner
Date: 12-6-89

APPROVED BY:

Roman J. Pienta, Ph.D.
Department Manager
Dynamac Corporation

Signature: Roman J. Pienta
Date: 12-6-89

Willial Greear, M.P.H.
EPA Reviewer, Section II
Toxicology Branch I
(H-7509C)

Signature: William D Greear
Date: 12/11/89

Marion Copley, D.V.M.,
D.A.B.T.
EPA Section Head
Section II
Toxicology Branch I
(H-7509C)

Signature: M Copley
Date: 12/12/89

DATA EVALUATION RECORD

CHEMICAL: Quinclorac.

STUDY TYPE: Mutagenicity--Rec assay with Bacillus subtilis.

MRID/ACCESSION NUMBER: 410635-32.

TEST MATERIAL: Registration No. 150 732.

SYNONYM/CAS NUMBER: 3,7-Dichloro-8-quinolinecarboxylic acid; BAS 514 H.

SPONSOR: BASF Corporation Chemical Division, Parsippany, NJ.

TESTING FACILITY: Hazleton Biotechnologies, Landjuweel, the Netherlands.

TITLE OF REPORT: Mutagenicity Evaluation of BAS 514..H in the Rec-Assay with Bacillus subtilis.

AUTHOR(S): Hoorn, A.J.W.

STUDY NUMBER(S): 87/0025.

REPORT ISSUED: October 16, 1986.

CONCLUSIONS/EXECUTIVE SUMMARY: Three nonactivated and three S9-activated Bacillus subtilis rec assays were conducted with eight concentrations of Reg. No. 150 732 ranging from 1 to 10,000 µg/plate. Under nonactivated conditions, the highest assayed dose (10,000 µg/plate) was cytotoxic but did not cause preferential inhibition of B. subtilis M45 (rec^-) compared to B. subtilis H17 (rec^+). However, in two of three trials, the nonactivated positive control, 5 µL/plate methylmethane sulfonate (MMS) failed to meet the minimum required response (≥4 mm difference between M45 and H17), for a positive result. In the only successful trial, MMS induced differential inhibition that only slightly exceeded the expected response. Therefore, we assess that the nonactivated results are unacceptable because the ability to evaluate between genotoxic and cytotoxic responses was only marginal.

The S9-activated assays were compromised for the following reasons:

1. No inhibition of either the repair-competent or repair-deficient B. subtilis strains was observed at any S9-activated dose. Since cytotoxicity is the only endpoint measured in this assay, the inability to demonstrate any response results in a "No Test."[1]

2. The sensitivity of the test system to detect the DNA-damaging activity of the S9-activated positive control was not adequately demonstrated.

3. Optimum conditions for interaction between the test material and S9 cofactor mix were not achieved. (See Section D, Reviewers' Discussion/Interpretation of Study Results.)

Furthermore, the study author did not provide analytical data to support the actual test material concentrations used in this study. We also assess that stock culture maintenance and verification of genetic markers were inadequate. We conclude, therefore, that the study is unacceptable.

Study Classification: The study is unacceptable.

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[1]Leifer, Z., Kada, T., Mandel, M., Zeiger, E., Stafford, R., and Rosenkranz, H. An evaluation of tests using DNA repair-deficient bacteria for predicting genotoxicity and carcinogenicity. A report of the U.S. EPA's Gene-Tox Program. Mutat. Res. 87(1981): 211-297.

A. MATERIALS:

1. Test Material:

Name:	Reg. No. 150 732 (ZNT No. 85/282-1)
Description:	White powder
Batch No.:	N57 III/2
Purity:	98.29%
Contaminants:	None listed
Solvent used:	Dimethylsulfoxide (DMSO)

Other comments: The test material was stored at room temperature in the dark. Based on the results of a solubility determination indicating that the test material had low solubility in water, DMSO was selected as the solvent for this assay. The stability of the test material in a unspecified aqueous solution was determined. Results of this analysis showed that no test material degradation occurred within 48 hours.

2. Indicator Organisms: Bacillus subtilis strains H17 (rec$^+$) and M45 (rec$^-$) were used for the rec assay and were obtained from T. Kada, National Institute of Genetics, Mishima, Japan. Stock cultures either were held frozen at -80°C or maintained at 4°C on nutrient agar. Cultures used in the assay were generated from the stocks and were grown overnight at 37°C. The report did not indicate that the genetic markers of the strains were verified.

3. S9 Activation: The S9 fraction, prepared from the livers of adult male Sprague-Dawley rats induced with Aroclor 1254, was purchased from an unidentified commercial source. The S9 mix contained 10% S9.

4. Positive Controls: The positive controls used in this assay were 5 µL/plate methylmethane sulfonate (MMS) without S9 activation and 100 µg/plate Sterigmatocystin (ST) with S9 activation.

B. STUDY DESIGN:

1. Rec Assay: For the rec assay, 2-mL volumes of top agar (0.1 M NaCl and 1.5% purified agar) were inoculated with 0.1 to 0.2 mL of the appropriate B. subtilis strain, mixed, and poured over the surface of nutrient agar plates.

The agar mixture was allowed to harden, and wells of uniform diameter were cut into the surface of each plate. For the nonactivated assay, 0.1 mL of a 0.2 M phosphate buffer, pH 7.4, was added to each well followed by the

addition of unspecified volumes of eight test material concentrations, the solvent, or positive control.

For the S9-activated assay, 0.5 mL of the S9 mix was incorporated into the agar overlay before pouring the mixture over the agar plates. Test material solutions and the negative and positive controls were introduced into the precut wells. Triplicate plates were prepared per strain, per treatment, per condition. The plates were incubated at 37°C for 24 to 48 hours; zones of inhibition around each well were measured and the diameter of each zone, if present, recorded in millimeters.

2. Evaluation Criteria: The assay was considered positive if a difference of 4 mm or greater was observed between the DNA repair-deficient M45 strain and the DNA repair-proficient H17 strain.

C. REPORTED RESULTS:

1. Rec Assay: Eight test material concentrations ranging from 1.0 to 10,000.0 µg/plate were assayed for DNA-damaging/repair activity in B. subtilis H17 and M45 in both the presence and absence of S9 activation. Three assays were performed. In the initial assay, the highest nonactivated dose (10,000 µg/plate) was cytotoxic as indicated by the comparable zones of inhibition that were scored for the DNA repair-competent (H17) and DNA repair-deficient (M45) strains. The remaining nonactivated doses were neither cytotoxic nor genotoxic. No inhibition was observed under S9-activated conditions. Both the nonactivated and S9-activated positive controls induced preferential inhibition of strain M45; however, the zone differential was less than four mm, the minimum zone difference required by the reporting laboratory to conclude a positive genotoxic response.

An independent repeat assay was performed with a comparable range of test material doses; however, the author did not consider these results to be valid because of the poor performance of the positive controls. We noted that there was no appreciable difference between the positive control finding of the initial and this repeated test. We further noted that the evidence for cytotoxicity at 10,000 µg/mL-S9 was not reproduced in the second trial. For the third trial, only the three highest doses (2500, 5000, and 10,000 µg/plate) were assayed. The highest nonactivated dose was cytotoxic, but no zones of inhibition were induced by S9-activated 10,000 µg/plate. Although the nonactivated positive control (5 µL/plate MMS) induced a minimum genotoxic effect, the preferential inhibition index for S9-

activated 100 µg/plate ST was less than the expected and required 4-mm difference.

Representative results from the three assays are presented in Table 1. Based on the findings from the three assays, the study author concluded that test material, BAS 514..H, ZNT No. 85/282-1, was not genotoxic in this test system.

D. REVIEWERS' DISCUSSION/INTERPRETATION OF STUDY RESULTS:

We assess that only the findings of the third nonactivated trial with test material, Reg. 150 732, indicated that the nonactivated test material at 10,000 µg/mL was cytotoxic but not genotoxic in the B. subtilis rec assay.

However, the nonactivated positive control, MMS, was a poor choice to demonstrate differential sensitivity. As indicated from the results of the first two assays as well as the findings from the third assay, MMS either did not induce definitive preferential inhibition or induced differential inhibition that only slightly exceeded the minimum required response. Therefore, the ability to differentiate between genotoxic and cytotoxic responses was marginal.

The S9-activated assays were unacceptable for the following reasons:

1. Cytotoxicity (equivalent or preferential) is the only end point measured in the rec assay; hence if a cytotoxic response cannot be demonstrated, the assay is considered a "No Test." A "No Test" results when a test material yields no zone of inhibition at the highest achievable dose. Leifer et al.[2] recommended that chemicals that yield a "No Test" in the agar diffusion procedure should be retested in a liquid suspension.

2. The ability of the test system to demonstrate the DNA-damaging activity of S9-activated ST was not adequately shown.

3. The S9-cofactor mix and the test material should have been mixed in the well to ensure contact between the test material and S9 enzymes. Adding the S9 mix to the agar overlay rather than mixing it with the test material did not provide optimum conditions for activation. As indicated by the study author, the test material had low

[2]Leifer et al. Mutat. Res. 87(1981): 211-297.

TABLE 1. Results of the B. subtilis Rec Assay With Test Material, Reg. No. [illegible] 732

Substance	S9 Activation	Dose per Plate	B. subtilis Strains[a] H17	M45	Preferential Inhibition Index[b]
Solvent Control					
Dimethylsulfoxide	-[c]	--	0.0 ± 0.0	0.0 ± 0.0	0.0
	+[c]	--	0.0 ± 0.0	0.0 ± 0.0	0.0
	-[d]	--	0.0 ± 0.0	0.0 ± 0.0	0.0
	+[d]	--	0.0 ± 0.0	0.0 ± 0.0	0.0
	-[e]	--	0.0 ± 0.0	0.0 ± 0.0	0.0
	+[e]	--	0.0 ± 0.0	0.0 ± 0.0	0.0
Positive Controls					
Methylmethane sulfonate	-[c]	5 µL	21.0 ± 0.0	24.3 ± 0.6	3.3
	-[d]	5 µL	22.3 ± 0.6	25.3 ± 0.6	3.0
	-[e]	5 µL	24.7 ± 0.6	29.0 ± 1.0	4.3[f]
Sterigmatocystin	+[c]	100 µg	17.3 ± 0.6	20.7 ± 0.6	3.4
	+[d]	100 µg	18.3 ± 0.6	20.7 ± 0.6	2.4
	+[e]	100 µg	18.0 ± 0.0	20.3 ± 0.6	2.3
Test Material					
Reg. No. 150 732	-[c]	10,000[g]	12.3 ± 0.6	15.7 ± 0.6	3.4
	-[d]	10,000	0.0 ± 0.0	0.0 ± 0.0	0.0
	-[e]	10,000	2.3 ± 0.6	11.7 ± 0.6	9.4
	+[c]	10,000	0.0 ± 0.0	0.0 ± 0.0	0.0
	+[d]	10,000	0.0 ± 0.0	0.0 ± 0.0	0.0
	+[e]	10,000	0.0 ± 0.0	0.0 ± 0.0	0.0

[a] Zone (diameter) of inhibition (mm) ± standard deviation; results from triplicate plates.

[b] Preferential Inhibition Index = Zone of Inhibition (M45)-Zone of Inhibition (H17); calculated by our reviewers.

[c] Initial Assay.

[d] Second Assay.

[e] Third Assay.

[f] Results for the remaining doses (1, 10, 100, 500, 1000, 2500, and 5000 µg/plate in the first and second trials and 2,500 and 5000 µg/plate in the third trial) were negative.

[g] Conforms to the reporting laboratory's criteria for a positive response (i.e., ≥ 3 mm difference between strains M45 and H17).

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solubility in water. It must, therefore, be assumed that the solutions prepared in DMSO could not readily diffuse from the wells and come in contact with either the S9 mix or the tester strains.

Furthermore, strain maintenance and verification of the genetic markers were inadequate to ensure against genetic changes that could affect the fidelity of the assay. Ideally, B. subtilis strains should be maintained as spores.

We also assess that the lack of analytical data to support the actual test material concentrations used in these assays renders the overall study unacceptable.

E. QUALITY ASSURANCE MEASURES: A signed but undated Quality Assurance statement was provided.

F. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 009-0012.

APPENDIX A

Materials and Methods

CBI pp. 009-0012.

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Page_____ is not included in this copy.

Pages 303 through 306 are not included.

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____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

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____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

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____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

APPENDIX A

Materials and Methods

CBI pp. 009-0012.

Ms. Caroline Gordon
Health Effects Division - CM2 - Room 821
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, Virginia 22202

Dear Ms. Gordon:

Enclosed is an initial draft for the following DER--QUINCLORAC:

- Mutagenicity--Rec assay with Bacillus subtilis. Study No. 87/0025. MRID No. 410635-32. Dynamac No. 247-J. EPA No. 2-47J.

We have enclosed the confidential business information for the above report.

Sincerely,

DYNAMAC CORPORATION

Robert J. Weir, Ph.D.
Program Manager

RJW/kp

Enclosure

EPA No.: 68D80056
DYNAMAC No.: 247-F
TASK No.: 2-47F
December 7, 1989

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Chinese Hamster Ovary Cell/HGPRT Forward Mutation Assay

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: [signature]

Date: 12-7-89

309

EPA No.: 68D80056
DYNAMAC No.: 247-F
TASK No.: 2-47F
December 7, 1989

DATA EVALUATION RECORD

QUINCLORAC

Mutagenicity--Chinese Hamster Ovary Cell/HGRPT Forward Mutation Assay

REVIEWED BY:

Nancy E. McCarroll, B.S.
Principal Reviewer
Dynamac Corporation
Signature: Nancy E. McCarroll
Date: 12-7-89

I. Cecil Felkner, Ph.D.
Independent Reviewer
Dynamac Corporation
Signature: I. Cecil Felkner
Date: 12-8-89

APPROVED BY:

Roman Pienta, Ph.D.
Department Manager
Dynamac Corporation
Signature: Roman J. Pienta
Date: 12-8-89

William Greear, M.P.H.
EPA Reviewer, Section II
Toxicology Branch I
(H-7509C)
Signature: William B. Greear
Date: 12/12/89

Marion Copley, D.V.M., D.A.B.T.
EPA Section Head, Section II
Toxicology Branch I
(H-7509C)
Signature: Marion Copley
Date: 1/2/90

DATA EVALUATION RECORD

CHEMICAL: Quinclorac.

STUDY TYPE: Mutagenicity--Chinese hamster ovary cell/HGPRT forward mutation assay.

MRID\ACCESSION NUMBER: 410761-02.

TEST MATERIAL: Registration No. 150 732.

SYNONYM/CAS NO.: 3,7-Dichloro-8-quinolinecarboxylic acid: BAS 514 H.

SPONSOR: BASF Corporation Chemical Division, Parsippany, NJ.

TESTING FACILITY: BASF Aktiengesellschaft; Ludwigshafen, W. Germany.

TITLE OF REPORT: Report on a Point Mutation Test carried out on CHO Cells (HGPRT Locus) with the Test Substance Reg. No. 150 732 (BAS 514H).

AUTHOR(S): Jackh, R.

STUDY NUMBER(S): 86/0214.

REPORT ISSUED: July 18, 1986.

CONCLUSION(S) - EXECUTIVE SUMMARY:

Six doses of test material, Reg. No. 150 732 (46.4, 100, 215, 464, 1000, and 2150 µg/mL), prepared in tissue culture medium, were assayed in the Chinese hamster ovary cell forward mutation assay, both under nonactivated and S9-activated conditions. The highest dose (2150 µg/mL/+/-S9) was severely cytotoxic. Three nonactivated assays were performed; results indicated that regardless of the reported concentrations, consistently increased mutation frequencies were seen at test material levels yielding cloning efficiencies of 50 to 60%; a dose-related response was not demonstrated. The inability to draw definitive conclusions results from the use of an unsuitable solvent (the test material is extremely insoluble in aqueous solutions); hence, preparation of accurate dosing solutions was severely limited. We conclude, however, that the findings suggest a possible mutagenic effect and, therefore, classify the nonactivated test material as presumptively positive (see Section D, Reviewers' Discussion/Interpretation of Study Results).

Although no evidence of a mutagenic response was uncovered in the S9-activated phase of testing, the results are unacceptable because of the use of excessive S9 (30%) in the S9-cofactor mix. Unless the study author can justify the use of a high liver enzyme level, the study should be repeated using an appropriate screening concentration of S9 (10% S9 in the S9-cofactor mix).

Additionally, there were no analytical data to support actual test material concentrations in solution, and a Quality Assurance statement was not provided.

Study Classification: The study is unacceptable and should be repeated using a more suitable solvent for the test material and the appropriate screening concentration of S9 in the S9 reaction mixture.

A. MATERIALS:

1. Test Material:

Name:	Reg. No. 150 732/BAS 514 H
Description:	Colorless crystalline powder
Batch No.:	N 32
Purity:	96.5%
Contaminants:	None listed
Solvent used:	Hams' F12 medium
Other comments:	The test material was stored at refrigerator temperatures. The test material was reported to have low aqueous solubility, and the pH of a 1% aqueous suspension was listed as 3.25. The report did not indicate whether the pH of the tissue culture medium was determined or adjusted to compensate for the low test material pH.

2. Test System: Chinese hamster ovary (CHO) cells, subclone K1, were obtained from Flow Laboratories, Meckenheim, W. Germany. Monolayers, seeded at a density of 1 x 10 cells, were maintained in Hams' F12 medium supplemented with 10% fetal calf serum, L-glutamine, and antibiotics.

3. S9 Activation: The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with Aroclor 1254. The S9-cofactor mix contained 30% S9 liver homogenate

4. Positive Controls: A final concentration of 50 µg/mL bromodeoxyuridine (BrdU) was used as the nonactivated positive control, and 10 µg/mL (final concentration) of 3-methylcholanthrene (3-MCA) was used as the S9-activated positive control.

B. TEST PERFORMANCE:

1. Preliminary Cytotoxicity Assay: The preliminary cytotoxicity assay was conducted with a concentration range of 1 to 10.000 µg/mL. Cells were exposed for 1[illegible] hours; no further details were provided.

2. Mutagenicity Assay: Cultures, seeded at 1 x 10[illegible] cells, were treated in the presence or absence of S9 activation with six levels of the test material (46.4 to 2150 µg/mL), the negative control (F12 medium), or the positive controls (BrdU at 50 µg/mL/-S9; 3-MCA at 10 µg/mL S9).

After a 4-hour exposure, cells were washed, suspended in fresh medium, reincubated, and plated at two cell densities. Cytotoxicity was determined by plating 200 cells in duplicate; cultures were incubated for 9 days, stained with methanol/Giemsa, and counted. Cells were also seeded in duplicate at a density of 10^5 cells/flask to allow expression of mutations. Throughout the 9-day expression period, cells were subcultured and reseeded at 10^5 cells. Mutant selection was accomplished by plating 3 x 10^5 cells/flask (five flasks) in medium containing 10 µM 6-thioguanine. Viability at selection was determined by seeding 200 cells/flask (two flasks/treatment) in complete medium. Selection and viability cultures were incubated for 9 days, fixed, stained with Giemsa, and counted. Cloning efficiencies (CE) and mutation frequencies (MF) were determined.

3. Evaluation Criteria:

a. Assay Validity: For the assay to be considered valid, the following criteria must be satisfied: 1) the CE for the nonactivated negative control must be between 70 and 115%, and the CE for the S9-activated negative control must be ≥50%; 2) the background MF for the negative control must be <15 x 10^{-6}; 3) the MF for the positive controls must be clearly elevated; 4) a minimum of four test doses ranging from noncytotoxic to cytotoxic should be available for analysis; and 5) the highest dose should exhibit a reduced CE.

b. Positive Response: The test material was considered positive if the MF exceeded the background MF by a factor of two and showed a consistent dose-response relationship.

C. REPORTED RESULTS:

1. Preliminary Cytotoxicity Assay: The study author stated that cytotoxicity was achieved at dose levels >2150 µg/mL but <4640 µg/mL; no further information was provided. Based on the results, the six doses selected for the mutation assay were 46.4, 100, 215, 464, 1000, and 2150 µg/mL with and without S9 activation.

2. Mutation Assay:

Nonactivated Assay: Three nonactivated trials were conducted with the test material. In the initial assay, no cells survived exposure to the highest assayed dose. For the remaining nonactivated doses, percent CE ranged from 41.75% at 1000 µg/mL to 69.0% at 46.4 µg/mL. Mutant colonies were recovered from cultures exposed to 46.4, 100, 464, or 1000 µg/mL. However, 25 mutant colonies were counted from cultures treated with 215 µg/mL of the test material (Table 1). The study author claimed that the increased MF (16.7 x 10^{-6} cells) was only slightly above "the borderline value of 15 x 10^{-6}", but failed to correct the MF for cytotoxicity. The MF calculated by our reviewers with an adjustment for cytotoxicity was 29.7 x 10^{-6}. The nonactivated assay was repeated using a comparable range of test material concentrations. As shown in Table 1, MFs calculated by our reviewers were considerably higher than those reported by the study author. At 46.4, 100, and 215 µg/mL, MFs adjusted for cytotoxicity were 5.8, 29.4, and 14.4 x 10^{-6}, respectively. Although the response was not clearly dose related, the MF at 100 µg/mL (29.4 x 10) was comparable to the MF observed at 215 µg/mL in the

TABLE 1. Representative Results of the Nonactivated CHO Forward Mutation Assays with Test Material, Reg. No. 150 732

Substance	Dose (μg/mL)	Percent Cloning Efficiency	Total Mutant Colonies/ 5 dishes	Mutation Frequency[a] x 10^{-6}	
Solvent Control					
Hams' F12 Medium	--[c]	70.25	0	0	0 [b]
	--[d]	76.25	0	0	0
	--[e]	67.75	0	0	0
Positive Control					
Bromodeoxyuridine	50[c]	55.25	229	152.7	275.9
	50[d]	45.25	121	80.7	177.4
	50[e]	36.50	67	44.7	122.2
Test Material					
Reg. No. 150 732	215[c,f]	56.00	25	16.7	29.8
	46.4[d,g]	57.50	5	3.3	5.7
	100.0	56.75	25	16.7	29.4
	215.0	50.50	11	7.3	14.4
	46.4[e,h]	65.75	3	1.8	2.7
	100.0	60.75	46	30.7	50.7
	215.0	64.00	0	0	

[a]Mutation frequencies presented by the author were not corrected for cytotoxicity

[b]Mutation frequency in [illegible]

$$\frac{\text{Total number of mutant colonies}}{\text{No. of dishes (5) x No. of cells plated for selection (3 x } 10^5 \text{) x Cloning Efficiency, calculated by our reviewers.}}$$

[c]Results from the initial assay.

[d]Results from the second assay.

[e]Results from the third assay.

[f]In the initial assay, no mutant colonies were recovered at the lower [illegible] and 100 μg/mL) or at the higher (464, 1000, and 2150 μg/mL) doses.

[g]In the second assay, no mutant colonies were recovered at the higher doses (46.4, 1000, and 2150 μg/mL).

[h]In the third assay, no mutant colonies were recovered at 464 or 1000 μg/mL; although mutant colonies were recovered at 2150 μg/mL, the cloning efficiency at this level was 4.5%.

first assay. The assay was repeated a third time, and increased MFs were achieved at 46.4 µg/mL (7.0×10^{-5}) and at 100 µg/mL (50.5×10^{-6}). The study author interpreted these results as not indicative of a mutagenic effect.

Results from the S9-activated assay are shown in Table 1. The highest assayed dose was completely cytotoxic. The percent CE for the remaining doses ranged from 7.5% at 1000 µg/mL to 63.5% at 46.4 µg/mL. No mutant colonies were observed at any assayed dose level; therefore, the MF for all treatment groups was zero.

Based on the overall results of the three nonactivated and the one S9-activated assay, the study author concluded that test material, Reg. No. 150 732, was not mutagenic in this test system.

C. REVIEWERS' DISCUSSION/INTERPRETATION OF STUDY RESULTS: We assess that several factors contribute to the difficulties in interpreting the nonactivated results from the CHO forward mutation assay conducted with the test material, Reg. No. 150 732.

1. The study author reported that the test material has low aqueous solubility but did not provide specific solubility information. According to the Farm Chemicals Handbook (1989), the solubility of Quinclorac in water is ≈61 µg/mL. The use of aqueous-based tissue culture medium as the solvent is, therefore, inappropriate. Similarly, the accuracy of the dosing solutions prepared from the stock "solution" (50 mg of test material [illegible] of tissue culture medium) is questionable. Since no information on the levels of solubility or precipitation were provided, it is conceivable that the achieved concentrations that showed a mutagenic effect (100 and 215 µg/mL) were essentially equivalent, and that the ability to demonstrate dose responsiveness was severely limited because accurate dosing solutions could not be prepared. The data do, however, suggest that regardless of the accuracy of the reported dose, mutagenic activity occurred within the range of test material concentrations causing 40 to 50% cytotoxicity.

2. The failure by the study author to correct the data for cytotoxicity is a major reporting deficiency. MFs calculated by our reviewers are, as expected, considerably higher than those reported by the study author and well within the range that should be considered suspect. The reproducibility of the increased MF in conjunction with the consistently zero MF for the negative controls provides further evidence that the

TABLE 2. Representative Results of the S9-Activated CHO Forward Mutation Assays with Test Material, Reg. No. 150 732

Substance	Dose (μg/mL)	Percent Cloning Efficiency	Total Mutant Colonies/ 5 dishes	Mutation Frequency[a] x 10^{-6}	
Solvent Control					
Hams' F12 Medium	--	67.75	0	0	[illegible][b]
Positive Control					
3-Methylcholanthrene	10	61.75	266	178.7	(288.1
Test Material					
Reg. No. 150 732	464[c]	67.5	0	0	
	1000[d]	[illegible]5	0	0	

[a]Mutation frequencies presented by the author were not corrected for cytotoxicity.

[b]Mutation frequency in ( )

$$= \frac{\text{Total number of mutant colonies}}{\text{No. of dishes (5) x No. of cells plated for selection (3 x } 10^{5}\text{) x Cloning Efficiency; calculated by our reviewers.}}$$

[c]No mutant colonies were recovered from cultures exposed to lower test material doses (46.4, 100, or 215 μg/mL).

[d]Highest assayed dose (2150 μg/mL) was completely cytotoxic

results are not artifactual and may be indicative of mutagenicity. The sensitivity of the system to detect mutagenesis appeared to be adequate since the MFs for the positive controls were markedly increased.

3. Considering that the study author reported that the pH of a 10% aqueous solution of the test material was 3.25, the possible effect of acidity due to the low pH should have been investigated.

With respect to the S9-activated assay, the concentration of S9 in the S9 cofactor mix (30%) was excessive. The general screening concentrations of S9 used in mammalian cell assays is ≤10%. Unless the study author can justify the need for high liver enzyme levels, the use of 30% S9 is not an acceptable practice.

We conclude, therefore, that the study is unacceptable and should be repeated. We further assess that the findings with the nonactivated test material are sufficient to warrant classification of Reg. No. 150 732 as presumptively mutagenic in this test system. We recommend that the repeat assay utilize a different solvent and be performed with a lower concentration of S9 in the S9 reaction mixture. It is not possible to recommend the dose range that should be reevaluated because the cytotoxic and possible mutagenic response(s) may differ significantly when the test material is prepared in a more suitable solvent. It is conceivable, however, that several assays may be required before definitive results are achieved.

E. QUALITY ASSURANCE MEASURES: A quality assurance statement was not provided.

F. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 0012-0020.

APPENDIX A

Materials and Methods
CBI pp. 0012-0020

APPENDIX A

Materials and Methods
CBI pp. 0012-0020

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EPA No.: 68D80056
DYNAMAC No.: 247-A
TASK No.: 2-47A
February 6, 1990
35-1

DATA EVALUATION RECORD

QUINCLORAC

Metabolism Study in Rats

STUDY IDENTIFICATION: Hawkins, D. R., Kirkpatrick, D., Dean, G. M., Whitby, B. R., Biggs, S. R. The biokinetics and metabolism of ^{14}C-BAS 514 H in the rat. (Unpublished report No. 86/5013 prepared by Huntingdon Research Centre Ltd., Huntingdon, England, for BASF Corporation Chemicals Division, Parsippany, NJ; dated January 14, 1987.) MRID No. 410635-33.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: William L. McFeeters for
Date: 2-5-90

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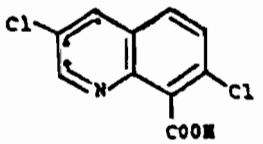
1. CHEMICAL: Quinclorac; BAS 514 H; 3,7-dichloro-8-quinoline-carboxylic acid.

2. TEST MATERIAL: [2,3,4-^{14}C]Quinclorac was from preparation numbers 155/42/12 and 155/42/13 with specific activities of 9.74 Ci/mol and radiochemical purities of ≥95.3. The chemical structure and radiolabeled carbons (denoted by asterisks) of quinclorac are as follows:



3. STUDY/ACTION TYPE: Metabolism study in rats.

4. STUDY IDENTIFICATION: Hawkins, D. R., Kirkpatrick, D., Dean, G. M., Whitby, B. R., Biggs, S. R. The biokinetics and metabolism of ^{14}C-BAS 514 H in the rat. (Unpublished report No. 86/5013 prepared by Huntingdon Research Centre Ltd., Huntingdon, England, for BASF Corporation Chemicals Division, Parsippany, NJ; dated January 14, 1987.) MRID No. 410635-33.

5. REVIEWED BY:

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Date: January 31, 1990

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Date: 2/13/90

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11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

1) Several batches of dosing solutions with different specific activities were prepared using appropriate amounts of the ^{14}C-labeled and unlabeled compound. Fourteen experiments involving oral administration of the compound by gavage and two experiments involving oral administration of the compound in the diet were conducted. Dosing solutions were prepared by suspending the appropriate amounts of [^{14}C]quinclorac in aqueous sodium carboxymethylcellulose solution (1.5 percent; w/v). Animals received approximately 1 mL of the appropriate dosing solution by gastric intubation. The total radioactivity administered was determined by radioassaying aliquots from the dosing solution. Test diets were prepared by thoroughly mixing the required amounts of [^{14}C]quinclorac and diet. The amount of radioactivity in the diet and its homogeneity were checked by radioassaying 10 portions of the diet.

2) Adult CD rats (strain not specified), each weighing 200 g, were obtained from Charles River, Margate, Kent. Male rats were 7 weeks old, and females were 10 weeks old.

3) The following oral gavage studies were conducted:

a. Preliminary studies: Two rats/sex received single oral doses of [^{14}C]quinclorac at 600 mg/kg and were housed individually for 5 days. Urine, feces, and expired air were collected at various intervals postdosing and radioassayed. In addition, one rat/sex received a single dose of [^{14}C]quinclorac at 15 mg/kg, and only expired air was collected for a period of 24 hours postdosing and radioassayed.

b. Biodisposition studies: Groups of five rats/sex received single oral doses of [^{14}C]quinclorac at 15 or 600 mg/kg or at 15 mg/kg following the administration of unlabeled quinclorac in single oral doses at 15 mg/kg/day for 14 days. Following dosing, animals were placed in individual glass metabolism cages, and urine and feces were collected separately at various intervals. Animals were sacrificed after 5 days, and the following tissues were collected: liver, kidneys, heart, lungs, brain, gonads, spleen, pancreas, adrenals,

7. CONCLUSIONS:

The metabolism of quinclorac ([2,3,4-^{14}C]3,7-dichloro-8-quinolinecarboxylic acid) following oral administration was studied extensively in male and female CD rats. The compound was rapidly absorbed and eliminated in the urine following administration of single oral doses of [^{14}C]quinclorac at 15 or 600 mg/kg and at 15 mg/kg after the animals were dosed with unlabeled quinclorac at 15 mg/kg/day for 14 days. Elimination in the urine 5 days after dosing accounted for 91 to 98 percent of the dose with only 1 to 4 percent eliminated in the feces. No radioactivity was detected in expired air. Biliary excretion was significant (11.5 to 14.5 percent of the dose) in animals receiving 600 mg/kg. However, most of this radioactivity was reabsorbed from the intestines and eliminated in the urine. Most of the radioactivity in the bile is associated with the glucuronide conjugate of quinclorac. The conjugate is apparently hydrolyzed in the intestines and reabsorbed. Almost all the radioactivity in the urine is unchanged quinclorac. Radioactive tissue residue levels 5 days after dosing were dose-dependent. Results from these and other (whole-body autoradiography and time-course) studies indicate that quinclorac may accumulate in the adrenal glands, bone marrow, thyroid, squamous epithelium of the non-fundic stomach, and ovaries. In 7-day time-course studies (oral gavage at 15 mg/kg/day or dietary at about 1,000 mg/kg/day) maximum ^{14}C residue levels were detected 30 minutes after the final dose; thereafter, residue levels decreased with time. Mean ^{14}C residues in plasma were also detected at 30 minutes in animals receiving single oral doses of 15, 100, or 600 mg/kg or 15 mg/kg/day for 7 days. Elimination was biphasic with half-lives of 3 to 4 hours for the rapid phase at the low doses and a half-life of about 13 hours at 600 mg/kg. Peak plasma levels of radioactivity in animals receiving higher doses (1200 mg/kg or 600 mg/kg/day for 7 days) were noted for 7 to 48 hours postdosing; saturation kinetics were also noted at these higher doses.

These studies are acceptable and fulfill EPA's guidelines series 85-1.

Items 8 through 10--see footnote 1.

---

[1]Only the items appropriate to this DER have been included.

thyroid, uterus, gastrointestinal tract and its contents, together with samples of bone-marrow, muscle and fat.

Urine samples collected at 0 to 8 and 8 to 24 hours postdosing were pooled by group and sex and extracted by digital chromatography using various solvents. The ethyl acetate extracts contained 93 to 100 percent of the total radioactivity and were further analyzed by thin-layer chromatography.

c. Biliary excretion studies: Groups of three rats/sex with bile duct cannulas received single oral doses of [^{14}C]quinclorac at 15 or 600 mg/kg. Bile was collected from each animal at 3-hour intervals over a period of 48 hours postdosing, whereas urine and feces were collected daily. Bile collected from an additional group of one rat/sex receiving 600 mg/kg was analyzed by digital chromatography and TLC as described for urine.

d. Plasma ^{14}C levels: Groups of five rats/sex received single oral doses of [^{14}C]quinclorac at 15, 100, 600, or 1200 mg/kg, and blood samples were withdrawn at various intervals postdosing. In addition, two groups of five rats/sex received 15 or 600 mg/kg/day for 7 days, and blood samples were collected at various intervals postdosing. The radioactivity found in plasma was then radioassayed by liquid scintillation counting (LSC). Plasma collected from additional groups of one rat/sex (except those receiving 1,200 mg/kg) 30 minutes after a single dose or the seventh dose was analyzed by digital chromatography or TLC as described above.

e. Tissue accumulation: For the quantitative tissue accumulation study, five rats/sex received single oral doses of [^{14}C]quinclorac at 15 mg/kg/day for 7 days. One male and one female rat were then killed at 0.5, 6, 24, 72, and 120 hours after the final dose, and various tissues were collected as described above. The livers and kidneys from one rat/sex receiving 15 mg/kg/day for 7 days were collected 30 minutes after the final dose. The tissues were homogenized and extracted with ethyl acetate, and the extract was analyzed by TLC.

Whole-body autoradiography was conducted with six male rats following the administration of [^{14}C]quinclorac in single oral doses at 15 mg/kg/day for 7 days. One rat was killed 24 hours after the first

dose and at 0.5, 6, 24, 72, and 120 hours after administration of the final dose. After sacrifice, animals were frozen and sagittal sections obtained at six levels through the carcass between the levels of the kidney and the spinal cord. The sections were freeze-dried and then placed in contact with X-ray film for 50 days at -15°C. The relative concentrations of radioactivity in the various tissues were assessed by visual inspection following development of the X-ray films.

4) In addition to the oral gavage studies described above, the following dietary studies were conducted:

a. Plasma ^{14}C levels: Groups of three rats/sex were fasted for an 8-hour period prior to being placed on the test diet for a period of 24 hours. The concentration of [^{14}C]quinclorac in the diet (15,000 ppm) was equivalent to a dose level of 1,200 mg/kg/day of test material administered to a 200-g rat consuming 16 g diet/day. Blood samples were collected before the animals were placed on the test diet and at 2, 4 or 6, 9, 12, or 18, 24, 42, and 66 hours after the animals were placed on the test diets.

b. Tissue accumulation: Six male and six female rats were placed on test diets for 7 days. The concentration of [^{14}C]quinclorac was equivalent to a dose level of 1,200 mg/kg/day of test material. One male and one female rat were killed at 0.5, 6, 24, 72, and 120 hours after the test diets were removed. Samples of blood and tissues were collected as described above. In addition, the livers and kidneys from one male and one female rat killed 30 minutes after they were removed from the test diets were trimmed, homogenized, and extracted with ethyl acetate, and the extract was analyzed by TLC.

B. Protocols:

No protocol was presented.

12. REPORTED RESULTS:

A. Gavage Studies:

1) Preliminary studies: Total recovery of radioactivity in animals receiving 600 mg/kg accounted for 98 to 100 percent of the administered dose at 5 days postdosing.

No radioactivity was detected in expired air after administration of [^{14}C]quinclorac at 15 or 600 mg/kg.

2. Biodisposition studies: Total recovery of radioactivity following administration of [^{14}C]quinclorac in a single dose at 15 or 600 mg/kg, as well as at 15 mg/kg following administration of unlabeled test material at 15 mg/kg/day for 14 days, accounted for 93 to 100 percent of the administered dose (Table 1). About 72 to 79 percent of the dose was eliminated 8 hours postdosing in the urine of rats receiving the low dose. Animals receiving the high dose eliminated most of the radioactivity within 24 hours following dosing with [^{14}C]quinclorac. Total elimination in the feces accounted for only 0.7 to 3.7 percent of the dose. Residues detected in the carcass 5 days after dosing accounted for $\leq$0.45 percent of the dose and were generally higher in females (Table 1). The highest residue levels were detected in the thyroid (<11 to <12 µg/g of the high dose), bone marrow (<2.6 to <4.0 µg/g of the high dose), and adrenal glands (<2.9 to <4.2 µg/g at the high dose); higher residue levels were detected in tissues of animals receiving the high dose when compared to tissues of animals receiving the low dose (Table 2).

Most of the radioactivity (71 to 85 percent) found in urine collected 0 to 24 hours postdosing was associated with unchanged parent compound in all three test groups (Table 3). Metabolite M1 accounted for 2.1 to 5.2 percent of the dose and was identified as the glucuronic acid conjugate of quinclorac. A second minor metabolite (M2) accounted for 0.2 to 3.9 percent of the radioactivity in the urine but was not identified.

Most of the radioactivity in the plasma 0.5 hours postdosing was also associated with the parent compound in animals receiving the 15 or 600 mg/kg dose (see also below).

3) Biliary excretion studies: The biodisposition pattern in bile duct-cannulated rats receiving 15 or 600 mg/kg of [^{14}C]quinclorac was similar to that noted above. Biliary excretion 2 days postdosing at 15 mg/kg accounted for about 1.1 and 2.9 percent of the dose in females and males, respectively, whereas in animals receiving the high dose, biliary excretion accounted for 11.5 and 14.5 percent, respectively. The timing of the maximum rates of ^{14}C excretion in the bile showed considerable interanimal variation.

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The major metabolite in bile identified following TLC analysis was the glucuronic acid conjugate of the parent compound (M1). Incubation of bile with β-glucuronidase resulted in the formation of the parent compound (Table 4). Incubation of bile in the absence of enzyme also resulted in the formation of the parent compound.

4) Plasma ^{14}C levels: The mean ^{14}C plasma levels in males and females receiving a single oral dose of 15, 100, or 600 mg/kg or 15 mg/kg/day for 7 days reached peak values at 30 minutes after dosing (Tables 5 and 6, Figures 1 and 2). Individual animal data showed large variability among individual groups with no consistent differences between sexes. However, mean plasma ^{14}C levels were dose-dependent. Peak ^{14}C levels in plasma of rats receiving a single dose of 1,200 mg/kg or repeated daily doses of 600 mg/kg/day for 7 days were reached 1 to 3 hours postdosing and remained at the same elevated levels for 48 and 7 hours, respectively. Elimination was biphasic, with elimination half-lives for the fast phase ranging from 3 to 4 hours at doses of 15 to 100 mg/kg and about 13 hours at 600 mg/kg (Table 7). Elimination half-lives for animals receiving 1,200 mg/kg or 600 mg/kg/day for 7 days were not calculated owing to the large variability between individual animals. Mean areas under the plasma radioactivity concentrations against time curves (AUC), normalized for dose level, indicated a linear increase in AUC with dose level over the range of 15 to 600 mg/kg. The AUCs for animals receiving repeated doses at 15 or 600 mg/kg or a single dose at 1,200 mg/kg were approximately twice as high as those calculated for the other doses, demonstrating a nonlinear increase in AUC in these groups.

Most of the radioactivity in the plasma from animals in all dose groups was associated with the unchanged parent compound (Table 8).

5) Tissue accumulation: The highest concentrations of ^{14}C in tissues of rats receiving 15 mg/kg/day for 7 days were found in animals killed 30 minutes after the final dose (Table 9). The highest concentrations were found in gastrointestinal tract, plasma, kidneys, and whole blood. Thereafter, the ^{14}C concentrations in tissues decreased with time after dosing and accounted

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TABLE 7. Elimination Half-lives of Radioactivity in Plasma of Rats After Various Oral Doses of [^{14}C]Quinclorac

Sex	Plasma ^{14}C Elimination Half-lives (hours) in animals receiving (mg/kg)[a]					
	15	7x15[b]	100	600	7x600[b]	1200
Male	2.9 ± 0.1	4.0 ± 0.4	3.6 ± 0.4	12.3 ± 1.7	--[c]	--
Female	3.2 ± 0.3	3.7 ± 0.4	4.1 ± 0.2	13.0 ± 1.7	--	--

[a]Based on elimination during the first 24 hours postdosing.

[b]Animals received a single dose daily for 7 days.

[c]Not determined owing to large variation between individual animals.

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for ≤0.11 μg/g tissue by 120 hours, except for ^{14}C residues in the adrenal gland, bone marrow, and thyroid, which were higher (≤0.82 μg/g).

Most of the radioactivity in the liver and kidneys (78 to 88 percent) of dosed animals was associated with unchanged parent compound. Metabolites M1 and M2 accounted for about 5 percent.

Whole-body autoradiography of male rats receiving 15 mg/kg/day for 7 days indicated maximum distribution of radioactivity 30 minutes after the final dose. Thereafter, radioactivity in tissues decreased with time. The results were in agreement with those obtained above for individual tissues, although whole-body autoradiography revealed relatively high levels of radioactivity in the squamous epithelium of the nonfundic stomach. As expected, the rat sacrificed 24 hours after receiving the first dose contained lower levels of radioactivity than the rat killed 24 hours after receiving seven doses.

B. Dietary Studies:

1) Plasma ^{14}C levels: The consumption of test diet was lower than expected, and the dose levels achieved ranged between 485 and 732 mg/kg in males and 333 between and 668 mg/kg in females. Plasma concentrations in females were lower than those found in males (Table 10). Peak ^{14}C levels in males and females were reached 18 hours and 12 hours, respectively, after the animals were placed on the test diets. Plasma levels decreased rapidly after the animals were removed from the test diet.

2) Tissue accumulation: The consumption of test diet on days 1 and 2 was lower than normal, but increased thereafter as the animals became accustomed to the diet. On days 3 to 7, the animals received dose levels ranging between 1,000 and 1,500 mg/kg/day for males and 880 and 1,000 mg/kg/day for females. The highest tissue concentrations were found in animals killed 30 minutes after discontinuation of the test diets (Table 11). The highest concentrations were found in plasma, kidneys, and gastrointestinal tract. Thereafter, the ^{14}C levels decreased with time; however, high levels were present in the adrenal glands, bone marrow, and thyroid at 120 hours after the test diets were removed.

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Most of the radioactivity present in the liver and kidneys of dosed animals (69 to 92 percent) was associated with the parent compound. However, in the liver, an unidentified metabolite, other than M1 and M2, was detected and accounted for 15 and 23 percent in females and males, respectively.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The results of the study showed that oral doses of [^{14}C]-quinclorac were almost completely absorbed when the compound was administered at nominal dose levels of 15 and 600 mg/kg, or at 15 mg/kg following 14 days pretreatment with nonradioactive compound. Mean urinary excretion of radioactivity accounted for more than 91 percent of the dose in both sexes after administration of any of the above doses, while mean fecal excretion ranged from 0.7 to 3.7 percent of the dose. The bile was a minor route of excretion of radioactivity after single 15-mg/kg doses (1 to 3 percent of the dose), but was found to be a significant route after single 600-mg/kg doses (11 to 15 percent of the dose). Very little radioactivity was excreted in the feces of intact rats dosed at this level, indicating that in the intact rat the greater part of biliary-excreted radioactivity was reabsorbed and eliminated via the urine.

Plasma kinetic studies indicated that radioactivity was rapidly absorbed after oral doses of [^{14}C]quinclorac at levels ranging from 15 to 1,200 mg/kg, with plasma concentrations of radioactivity at or near peak levels being reached 30 minutes after dosing. The decline in plasma radioactivity concentrations was apparently multiphasic, but the first phase of the decline resulted in concentrations dropping to a small proportion of peak levels, and in one experiment, falling to below the limit of detection during this initial phase. The half-lives that were calculated (and reported in the results section) were based on data points from the first phase of the decline, and no allowance was made for the contribution of the slower phases (which was probably negligible). After dosing at 15 or 100 mg/kg, plasma concentrations declined initially with half-lives of approximately 3 to 4 hours. Longer half-lives of approximately 12 to 13 hours were observed after single 600-mg/kg doses. However, AUCs increased in an approximately linear fashion with dose level (single doses) from 15 to 600 mg/kg. Above 600 mg/kg, the relationship between AUC and dose level was nonlinear, and AUCs at 1,200 mg/kg (normalized for dose) were approximately twice as high as would have been

predicted from a linear increase. After single oral 1,200-mg/kg doses, high plasma levels of radioactivity were maintained for more than 24 hours. This plateau effect also occurred to a slightly lesser extent after the last of seven daily 600-mg/kg/day oral doses. In both of these experiments, animals died presumably as a result of the toxic effect of the compound.

Tissue distribution studies showed that the radioactivity was widely distributed through body tissues after oral doses of [^{14}C]quinclorac, but generally at a much lower level than in circulating blood. Radioactivity was eliminated from most tissues at a rate similar to elimination from blood. At 5 days after single oral doses of [^{14}C]quinclorac were administered at either 15 or 600 mg/kg, radioactivity concentrations were below the limit of detection in almost all tissues. Some increased retention of radioactivity was observed after repeated daily administration at 15 mg/kg, but the effect was probably not very great. In this latter experiment, where a time course of samples was analyzed, it was found that radioactivity was eliminated more slowly from the thyroid and adrenal glands and the bone marrow than from the blood. Levels in the brain were very low. Whole-body autoradiography studies confirmed the results of the quantitative studies and confirmed that radioactivity levels in the central nervous system, in addition to the brain, were very low. An unsuspected concentration of radioactivity in the squamous epithelium of the nonfundic stomach was also revealed by whole-body autoradiography, for which no explanation can be offered. No similar concentration was observed in the intestinal mucosa.

Biotransformation apparently was not an important factor in the elimination of [^{14}C]quinclorac by rats. Oral doses at 15 or 600 mg/kg were excreted largely unchanged. However, analysis of bile from animals that had received [^{14}C]quinclorac at a level of 600 mg/kg revealed large amounts of the glucuronide conjugate of quinclorac. In intact rats, this conjugate was presumably hydrolyzed by the intestinal microflora, and the released quinclorac was reabsorbed and excreted via the kidneys. Glucuronide conjugate formation was presumably much less extensive after 15-mg/kg doses, where biliary excretion of radioactivity was much lower. No significant metabolites of quinclorac were observed in circulating plasma sampled at the time of peak concentrations, or in kidneys or livers from animals that had received seven daily oral 15-mg/kg doses of [^{14}C]quinclorac. However, livers from animals consuming a very high dietary dose of [^{14}C]quinclorac did contain an unknown metabolite that was not observed in any other sample.

B. A quality assurance statement was signed and dated November 30, 1987, by P.H.C.V. Richold. In addition, a GLP compliance statement for FIFRA standards was signed and dated January 14, 1987 by D. Kirkpatrick and D. N. Kellett.

14. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

These studies provide extensive information on the metabolism and biodisposition of quinclorac in rats following oral administration. The results from the various experiments support and corroborate each other. The studies were adequately conducted, and the authors' conclusions are supported by the data presented. Adequate numbers of animals were used in each experiment. One deficiency was noted in calculating plasma half-lives; these values were based on the fast phase and not the slow elimination phase. In addition, the accuracy of these calculations is questionable. It would have been interesting to evaluate the pharmacokinetics of absorption and elimination of quinclorac, particularly since an exhaustive study of plasma ^{14}C levels with time was conducted. However, these data would not change the conclusions of this study. Results of tissue residues strongly indicate bioaccumulation of radioactivity in the adrenals, bone marrow, thyroid, and squamous epithelium of the nonfundic stomach, as well as a possible accumulation in the ovaries. Consequently, a thorough analysis of data from chronic toxicity/oncogenicity studies should be performed to determine potential adverse effects. These studies fulfill EPA's requirements.

Items 15 and 16--see footnote 1.